Monitoring of Adrenal Functions Amid the COVID-19 Pandemic: Lessons From Pediatric Leukemia

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Introduction: Glucocorticoids are considered the cornerstone of the induction phase in all treatment protocols of acute lymphoblastic leukemia (ALL). Among the adverse effects of high-dose glucocorticoid treatment, adrenal insufficiency is secondary to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. This drawback of exogenous steroid therapy gains a contemporary particular relevance in the current era of the COVID-19 pandemic.

Methods: Thirty-two patients with ALL were recruited to participate in this study. Basal cortisol and adrenocorticotropic hormone (ACTH) levels were assessed before induction therapy and re-measured 7 days after steroid cessation. Patients with low cortisol levels were subjected to ACTH stimulation test and were followed up till recovery of ACTH axis.

Results: There was a significant decline in the cortisol levels after completion of glucocorticoids therapy in eight patients (25%), ($P<0.000$) and it returned to normal levels at the 28th post-induction day ($P<0.614$). However, two patients showed no response to ACTH testing and received replacement physiologic doses of daily hydrocortisone. A patient had febrile neutropenia and another one developed COVID-19 pneumonia, for both of them high-stress steroid doses have been administered. All the studied patients had normal cortisol levels at the end of the 4-week follow-up period.

Conclusions: We concluded that there might be a beneficial role of testing adrenal reserve in children with ALL; especially those at the maximum period of adrenal suppression. We highly recommend educating patients and families about early symptoms of adrenal insufficiency, assessing adrenocortical functions during the era of the COVID-19 pandemic, and implementing a prompt replacement therapy plan in order to avoid the catastrophic COVID-19-induced cytokine storm.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children and represents approximately 25% of cancer diagnoses among children younger than 15 years [1]. A dramatic improvement in the 5-year survival rate has been achieved for standard risk

pediatric ALL; reaching approximately 90 % [2]. Glucocorticoids were among the first drugs used in the treatment of ALL and undoubtedly contributed to improvements of outcome over the last decades and are considered the cornerstone of the induction phase in all treatment protocols. The main effects of these drugs are reduction of inflammation, immunosuppression, anti-proliferative and cytotoxic effects on cancerous cells, and induction of apoptosis of the lymphoblastic cells [3, 4]. Supra-physiological doses of glucocorticoids have been associated with many adverse systemic effects. One of the most worrisome and treatable effects is the suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Thus, the body's own glucocorticoid production may be suppressed; resulting in reduced cortisol response which is rarely clinically manifested. It is more commonly subtle and manifests as impaired cortisol response to stressful stimuli and inadequate host defense against infections; remaining a cause of morbidity and death [5, 6]. The time course of recovery of HPA after glucocorticoid therapy in children treated for ALL shows marked inter-individual variations [7]. Earlier studies have shown a varying incidence and duration of adrenal insufficiency as well as a controversy regarding the need for hydrocortisone substitution [5, 6]. The ideal time point of adrenal function assessment is during ALL therapy and the length of hydrocortisone substitution. Based on the current status of the widely spreading COVID-19 pandemic, it is highly indicated to explore the impact of exogenous corticosteroid therapy on adrenocortical axis function in immunocompromised children with ALL. The aim of this study was to assess the adrenal gland function in children with ALL before and after induction therapy with corticosteroids and to find out the prevalence and duration of adrenal insufficiency among them.

METHODS

This is a prospective study involving all newly diagnosed children with ALL during the period from December 2018 until the end of April 2020. Studied patients with pre-B acute lymphoblastic leukemia were recruited from the pediatric hematology/oncology ward at Sultan Qaboos University Hospital, Muscat, Oman. Ethics Committee at College of Medicine at Sultan Qaboos University approved the study protocol prior to the study (#1736 dated 9/Aug./2018) and written informed assents/consents were obtained from all patients or their legal guardians, wherever applicable. This research received no specific grant from any funding agency in the public, commercial or non-profit sectors. We excluded patients below the age of 12 months, patients whose parents refused to allow them to participate in the study, those who failed to complete the induction phase of chemotherapy until the end of the study, patients with previous adrenal disorders, and those with a history of steroid intake before the diagnosis of leukemia. ALL patients were treated according to MRC UKALL 2011 protocol that includes the corticosteroid dexamethasone in induction therapy at a dose of 6 mg/m2/day for 28 days [8]. A full history of taking laying stress on past history of steroid intake for any other disease, family/past history of hypothalamic, pituitary/ adrenal gland related disorders were obtained from all patients. Additionally, a history of steroid withdrawal symptoms such as anorexia, vomiting, arthralgia, myalgia, abdominal pain, weight loss, and hypotension was taken as well. Laboratory investigations including complete blood picture (CBC) with differential blood count initially and during therapy phases, bone marrow aspirate, cytology, immunophenotyping, lumbar puncture with cerebrospinal fluid (CSF) cytology, liver and kidney functions, serum electrolytes, and random blood sugar were done initially and followed up during various stages of therapy. Adrenal function testing was compromised of basal adrenocorticotropin hormone (ACTH) and serum cortisol levels that were assessed at 8 am before the initiation and after discontinuation of glucocorticoid treatment in the induction phase of chemotherapy (each patient received a 28 days course of dexamethasone; 6 mg/m2/day followed by one-week tapering dose). Those who had low cortisol 7 days after induction therapy were subjected to a standard dose ACTH stimulation test. The test was performed in the morning between 08:00 and 09:00 am. Basal blood samples for cortisol (t=0) were taken. Tetracosactrin (Synacthen) was then administrated at a dose of 250 µg as an intravenous bolus. A blood sample was collected one hour later to measure cortisol level. A normal response was

defined as stimulated serum cortisol >500 nmol/L; corresponding to the threshold for the standard ACTH test in our laboratory. If peak cortisol level was below 350 nmol/L, then the patient would need to be on a regular dose of hydrocortisone 10 mg/m²/day and serum cortisol level would need to be followed up at days 14 and 28 after discontinuation of the dexamethasone and then every month until full recovery of the HPA axis.

RESULTS

A total of 32 ALL patients with a mean ± SD age of 5.9 ± 2.75 years and no other chronic diseases completed the study (20 of them were males). Twenty-six patients had a standard risk for ALL and 6 had preliminary CNS disease (Table 1). All patients were treated with UKALL 2011 protocol that includes dexamethasone induction therapy for 35 days (28 days full dose 6 mg/m2/day; followed by 7 days tapering). The initial hematological and biochemical characteristics of all patients at the diagnosis stage are summarized in Table 2.

Morning baseline cortisol levels before the start of chemotherapy were normal for all patients (above the cut-off value of 200 nmol/L). Baseline ACTH levels were within normal ranges.

Table 1: Demographic and Clinical Data of Studied Patients[a]

	Patients (n=32)
Gender, No.(%)	
Male	20(62.20)
Female	12(38.80)
Age, y	
Minimum – Maximum	2-13
Mean±SD	5.94±2.75
Median	5
Weight, kg	
Minimum – Maximum	9-29
Mean±SD	18.57
Median	19.80
Diagnosis, No.(%)	
Pre B ALL Standard Risk	26(81)
Pre B ALL Intermediate Risk	2(6)
Pre B ALL High Risk	4(13)
CNS Disease at Diagnosis	
No CNS Disease	26(81)
CNS Disease	6(19)

[a] Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system

There was a highly significant difference between the mean values of baseline cortisol levels and their values at day seven after the end of steroid tapering (P<0.000). Similarly, there was a significant

Table 2: Mean Hematological and Biochemical Values of the Study Patients [a]

	Measure	Median	Maximum	Minimum
Hemoglobin, Mean+SD	7.91+1.74	8.00	11.00	5.00
Platelets (×10⁹/L), Mean+SD	93+131.50	53	671	3
WBCs (×10⁹/L), Mean+SD	44+118.00	9	655	1.00
Neutrophils,% / ANC (×10⁹/L), Mean+SD	0.81+1.07	1.00	5.00	0.00
Creatinine, mmol/L	24	26	61	11
Sodium (N: 136-145 mmol/L)	136	135	129	135
ALT / AST, IU/L	20/41	14/22	55/45	15/11
CRP (N: up to 5 mg/L)	48	21	98	5

[a] Abbreviations: ALT, Alanine aminotransferase; ANC, absolute neutrophilic count; AST, aspartate aminotransferase; CRP, C reactive protein

Table 3: Baseline and Follow-Up Values of Serum Cortisol and ACTH of the Studied Patients[a]

	Baseline Cortisol, nmol/L	Baseline ACTH, pg/ml	F/U 1 Cortisol in Day 7	F/U 2 Weeks Day 14	F/U 3 Weeks Day 28	Paired T-test (Baseline and Day 7)	Paired T-test (Baseline and Day 28)	Paired T-test (D7 and Day 28)
Mean	389.00	29.05	240.97	318.34	408.44	<0.0001	0.6148	<0.0001
SD	167.18	21.90	95.50	92.03	138.98			
Median	349.00	24.90	232.50	300.50	417.50			
Minimum	212.00	1.00	10.00	141.00	212.00			
Maximum	822.00	91.20	427.00	480.00	617.00			

[a] Abbreviations: ACTH, adrenocorticotropin hormone

difference between the mean values of cortisol levels values at day seven and day 28 after the end of steroid tapering (P<0.000). There was no difference between the baseline and day 28 values after steroid tapering (P<0.614) (Table 3).

Of note, eight patients (25%) had low basal cortisol levels below 200 nmol/L and two of them (6.25%) had extremely low ranges (38 and 10 nmol/L, respectively). Five patients were in the standard risk, one in the intermediate-risk and two in the high-risk group. Eight patients had a normal response to ACTH stimulation tests, apart from two patients with extremely low values who had poor response to ACTH; indicating no adrenocortical reserve. Of these two patients, one had febrile neutropenia and another one developed COVID-19 pneumonia. Of note, the affected patient with COVID-19 was continued on the induction dose of dexamethasone for two weeks and then gradual tapering was done over another two weeks. He had no clinical or laboratory evidence of multisystem inflammatory syndrome in children (MIS-C). He required oxygen by mask with no assisted ventilation. The patient with febrile neutropenia received IV broad-spectrum antibiotics on day seven of sampling. He received high-stress doses of hydrocortisone for two weeks that was discontinued after clinical improvement.

Six patients had initial CNS disease. None of our patients received fluconazole prophylaxis. All the studied patients had normal cortisol levels at the end of the 4-week follow-up period. Table 4 shows that low cortisol levels at the seven post-induction day therapy were not statistically different in the three risk groups (P=0.169)

DISCUSSION

In the current work, adrenal insufficiency was defined as a low stimulated cortisol level that was detected in only 6.25% of our studied patients with ALL at the end of induction therapy; using dexamethasone. These patients had febrile neutropenia and sepsis. Because of their clinical condition, and extremely

low levels of cortisol with no increments after ACTH stimulation, they were given replacement therapy with physiological doses of hydrocortisone for one month until the recovery of the hypothalamic adrenal axis. Then, they received a high-stress dose during sepsis that was detrimental for their clinical recovery. All the 32 study patients had normal cortisol levels after 4 weeks of follow-up (day 56 of therapy). In earlier studies, authors reported variable but higher frequency of adrenal insufficiency between 20–70% in pediatric patients with ALL after the end of induction therapy [9, 10]. In these studies, replacement therapy with hydrocortisone was considered for patients with low values regardless of their clinical status. In a study by Rix M et al., significant laboratory and clinical manifestations of adrenal suppression (withdrawal symptoms and signs, weakness, fatigue, decreased appetite, weight loss, nausea, vomiting, diarrhea, and abdominal pain) were noted in only 3 (12%) patients. As the study was non-interventional, these patients were not treated with physiological doses of hydrocortisone and the patients continued receiving their leukemia treatment protocols [11]. More recently, Loimijoki et al., reported that in 64 ALL patients with proven adrenal insufficiency, hydrocortisone replacement therapy was discontinued in 53 cases (85%) despite the persistence of insufficient adrenal response in the stimulation test [12]; questioning the clinical value of its use in asymptomatic patients.

Of note, none of our patients had a septic shock or needed pediatric intensive care unit care during the study period. However, two patients with no adrenal reserve were started on high-stress doses of hydrocortisone. We believe that if the high-dose steroid was not started for these two patients, they would end up with intractable septic shock. Despite a large number of studies of the HPA axis and a large Cochrane systematic review [13], high doses of steroids are administered for induction therapy in patients with ALL. However, the currently available protocols have not included routine testing of patients

Table 4: Post Induction Day 7 Cortisol Level in Patients With ALL; Based on risk Group Stratification[a, b]

	Normal Cortisol Levels at Day 7	Low Cortisol Levels at Day 7	Total
Standard Risk	21	5	26
Intermediate Risk	1	1	2
High Risk	2	2	4

[a] Abbreviations: ALL, acute lymphoblastic leukemia
[b] Fischer Exact test was used between the 3 risk groups; P=0.169

for adrenal reserve, not even recommending the use of physiological doses of hydrocortisone after one week of tapering when the cortisol levels are lowered and adrenal suppression is maximized. A single morning serum cortisol reflects basal adrenal function but gives no indication of the capacity to respond to stress. Previous studies used stimulation tests in children with ALL after finishing four or six week courses of dexamethasone or prednisone. By using the standard ACTH test, Felner et al., found adrenal suppression lasting 2.5 to eight months in 41% of their patients [14]. Kuperman et al., found restoration of pituitary function after one week; while cortisol responses remained suppressed in 40% of children after two weeks [15]; whereas Cunha et al., reported pituitary recovery after two days and full adrenal recovery after one month [16]. Mahachoklertwattana et al., used the low-dose ACTH test and found adrenal suppression in 46% of their cases two weeks after stopping steroids [17]. In the current study, age, gender, and leukemia risk status had no relation to the low levels of basal or stimulated cortisol. This might be attributed to the low numbers of adrenal-suppressed patients. Another explanation is that all of our patients received a standardized equal dose of dexamethasone during the induction phase, regardless of their age, gender, or risk category. Considering the course of HPA axis recovery, young children like those in our series usually have a significantly earlier recovery. Mahachoklertwattana et al., explained this difference by the fact that it could be due to the difference in sensitivity of the HPA axis in response to negative feedback of exogenous corticosteroids [17].

Recently, the COVID-19 pandemic has affected more than 11 million people all over the world; claiming more than half a million lives. Although children seem to be relatively protected, immunocompromised pediatric patients with malignancy are at heightened risk [18]. Accumulating recent evidence proves that corticosteroids; especially dexamethasone has a crucial role in controlling COVID-19-associated cytokine storm and reduction of COVID-19-related mortality [19, 20]. In our study, only one patient was COVID-19 positive and he had the maximum adrenocortical suppression and needed dexamethasone continuation. Presumably, children with malfunctioning adrenocortical axis secondary to prolonged exogenous dexamethasone therapy

need prompt monitoring and proactive intervention to prevent catastrophic outcomes if a subset of them contracted COVID-19. Our study has several strengths points such as being prospective, continuing over more than one year, and including multiple testing points. Moreover, all the patients completed the study with no dropouts. However, study limitations include single-center experience and the small number of patients.

In conclusion, this prospective study demonstrated that there might be a beneficial role of testing adrenal reserve in children with ALL; especially if they have a risk of sepsis at the maximum period of adrenal suppression. Driven by the current COVID-19 status, we recommend educating patients and their families about early symptoms of adrenal insufficiency. Prompt replacement therapy is necessary for those patients with a suppressed adrenocortical axis. Regular monitoring and follow-up are needed till recovery of the intrinsic physiological pathways. For selected patients, repeated assessment is still required upon further administration of high-dose steroid

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICS APPROVAL

The research has been approved by the Medical Research and Ethics Committee (MREC) of Sultan Qaboos University (SQU)(SQU-EC/ 028/2017).

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