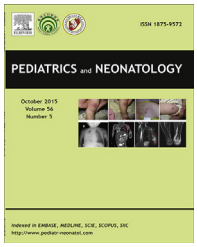
Pediatrics and Neonatology (2015) **56**, 339–345

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com



ORIGINAL ARTICLE

Risk Factors for Hyperglycemia During Chemotherapy for Acute Lymphoblastic Leukemia Among Taiwanese Children

Meng-Che Tsai [a], Hsin-Hui Huang [a], Yen-Yin Chou [a], Chao-Neng Cheng [a], Jiann-Shiuh Chen [a,*], Shio-Jean Lin [b]

[a] *Department of Pediatrics, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[b] *Department of Pediatrics, Chi-Mei Hospital, Tainan, Taiwan*

Received Sep 13, 2014; received in revised form Jan 6, 2015; accepted Jan 23, 2015
Available online 1 April 2015

Key Words
acute lymphoblastic leukemia;
chemotherapy;
children;
hyperglycemia;
Taiwan

Background: Hyperglycemia is common during treatment for pediatric acute lymphoblastic leukemia (ALL). Several risk factors have been proposed, but emergence of new evidence suggests conflicting results. In view of ethnic differences in the propensity for diabetes, this study aims to delineate the characteristics of pediatric patients at risk for hyperglycemia during chemotherapy in Taiwan.
Methods: This retrospective study involved chart review of consecutive patients younger than 18 years with diagnosis of ALL in a medical center in Taiwan from 1997 to 2008. Hyperglycemia was defined by random plasma glucose levels ≥200 mg/dL or fasting glucose levels ≥126 mg/dL in at least two separate samplings. Risk factors for hyperglycemia were described with crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) in the univariate and multivariate regression analysis.
Results: A total of 133 patients were included for analysis. Overall, 22 patients (16.5%) experienced hyperglycemia during ALL treatment. Most hyperglycemic episodes occurred within the first 8 days after prednisolone use. Age older than 10 years was the most important predictor of hyperglycemia (adjusted OR = 10.88, 95% CI 2.40–49.37). Patients with fasting glucose concentration ≥100 mg/dL were also 5.7-fold (95% CI 1.63–19.93) more likely to develop hyperglycemia, whereas the predictive significance of obesity was attenuated after adjustment.
Conclusion: Assessment of glucose concentration should be vigilant in the 1st week after prednisolone use during ALL treatment. Clinicians should be alert to the patient at risk of hyperglycemia, particularly obese adolescents with disarranged glucose homeostasis.

* Corresponding author. Department of Pediatrics, National Cheng Kung University Hospital, 138, Shengli Road, Tainan, Taiwan.
E-mail address: jian@mail.ncku.edu.tw (J.-S. Chen).

http://dx.doi.org/10.1016/j.pedneo.2015.01.008

1. Introduction

Overweight and obesity in childhood and adolescence have been implicated in association with various adverse health consequences.[1,2] The rising prevalence of obesity among children is an emerging problem of public health worldwide and Taiwan is no exception.[3] A particular concern for obesity in childhood is given to the increased likelihood of deregulation in glucose metabolism during and even after treatment for acute lymphoblastic leukemia (ALL).[4,5]

Hyperglycemia is a common occurrence in pediatric patients during induction chemotherapy of ALL.[6–8] The potential causes may include beta cell dysfunction caused by chemotherapeutic drugs such as L-asparaginase, increased insulin resistance and hepatic gluconeogenesis induced by corticosteroids, or synergistic effects of these medications, given that these pharmacological agents are usually combined during initial induction therapy.[4,5] The spectrum of hyperglycemia can range widely from transient isolated episodes to severe life-threatening complications such as diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar syndrome.[9–11] Transient hyperglycemia developed during this period largely resolves as the chemotherapy is discontinued.[12] However, affected children may need longer hospitalization and delay in chemotherapy; they may experience increased infective incidence and may even have poorer survival outcomes.[13,14] Recognizable risk factors for treatment-related hyperglycemia have been studied among children who are characterized by Down syndrome, older than 10 years of age, obese at the start of chemotherapy, classified in the higher risk group for ALL, and using native L-asparaginase.[5–7,12,13] However, several conflicting results in more recent studies have indicated the absence of significant associations between weight status and hyperglycemic episodes.[8,14–16]

Given the rising rate of obesity and overweight among Taiwanese children, in the past 10 years, those who receive treatment for leukemia may be at a higher risk for secondary hyperglycemia. Because ALL treatment protocol evolves over time, the side effects of therapy should be continually reevaluated. Few published data have referred to the epidemiology of treatment-related hyperglycemia in Asian pediatric patients with ALL.[17] The purpose of the current study is to evaluate the incidence and risk factors of hyperglycemia during the treatment for leukemia among Taiwanese children.

2. Materials and methods

This is a retrospective study involving a cohort of consecutive patients, age younger than 18 years, in whom ALL was diagnosed and who were admitted to National Cheng Kung University Hospital, Tainan, Taiwan, between January 1997 and December 2008. The hospital is a tertiary medical center for children with pediatric cancer diseases from Tainan and neighboring municipalities.

2.1. Variables and measures

Using the body mass index (BMI) growth chart among normative Taiwanese children beginning at 2 years of age, we excluded patients who were younger than 2 years.[18] Children with previously diagnosed diabetes mellitus (DM) or who were treated with glucocorticoids were also excluded. Medical records were reviewed to obtain relevant clinical data, including demographic information, such as age at diagnosis, sex, weight, height, and family history of diabetes as well as clinical parameters, such as initial white blood cell count (WBC), initial C-reactive protein (CRP) level, initial fasting glucose level, immunotyping of leukemic cells, risk classification, and outcome variables, such as leukemic relapse, death, and infective complications. Our standard practice is to admit all patients with fever or suspected vesicular skin lesions and to treat them with empirical antibiotics or antiviral agents accordingly. Infective complications were thus defined as occurrences of aforementioned episodes at any time of the entire chemotherapy regardless of clinical severity or identifiable pathogens after investigation. Family history of diabetes was defined by the presence of diabetes mellitus in patients' first- or second-degree relatives. Hyperglycemia was defined as at least two separate random plasma glucose levels $\geq$200 mg/dL or fasting glucose levels $\geq$126 mg/dL according to the published guidelines for childhood diabetes.[19] Fasting glucose concentrations were checked before chemotherapy and routinely as indicated during hospitalization. Moreover, patients with hyperglycemia or glucosuria received more intense monitoring for plasma glucose levels. BMI was calculated by dividing weight in kilograms by height in square meters. We determined the weight status according to the gender and age-specific BMI charts using the Taiwan reference data. BMI from the 5th percentile to less than the 85th percentile was classified as "healthy weight"; BMI from the 85th percentile to less than the 95th percentile was classified as "overweight"; and BMI greater than the 95th percentile was classified as "obesity".[18,20] The 1st day of treatment was designated when the use of steroids was started. The entire procedure was approved by the Institutional Review Board of National Cheng Kung University Hospital, Tainan, Taiwan.

2.2. Treatment regimens

All patients were treated according to the protocols of the Taiwan Pediatric Oncology Group (TPOG). Given that the study period spanned from 1997 to 2008, some modifications are worthy of mention in the TPOG protocols in 2002. Before 2002, patients in the standard-risk (SR) and high-risk (HR) groups received the treatment regimens of TPOG-ALL-93 SR/HR, and those with patients in the very-high-risk (VHR) groups received the treatment regimen of TPOG-ALL-97 VHR. After 2002, these protocols were merged as the TPOG-ALL-2002. In brief, patients in the SR group received a 5-week induction remission regimen that consisted of prednisolone, vincristine, and either epirubicin or L-asparaginase in the TPOG-ALL-93 SR/HR, whereas epirubicin was only used as the third chemotherapeutic drug in the TPOG-ALL-2002. In addition, an additional nine doses of L-asparaginase were concurrently administered in the remission induction treatment in the case of the HR patients. Although 300 mg/m^2 for SR patients and 600 mg/m^2 of etoposide for HR patients were given in the TPOG-ALL-93