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## ORIGINAL ARTICLE

# Growth Hormone Deficiency (GHD) as a neglected side effect of treatment in children with Acute Lymphoblastic Leukemia (ALL) and Non-Hodgkin's Lymphoma (NHL)

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**ABSTRACT**

*Acute lymphoblastic leukemia (ALL) is the most common childhood cancer and non-Hodgkin's lymphoma (NHL) is the most common childhood cancer. These children may suffer from some late effects of treatments such as endocrinopathies (thyroid, pituitary) and metabolism dysfunctions. Growth Hormone Deficiency (GHD) is one of the causes of short stature. We studied 50 children with ALL (n=25) or NHL (n=25) in a 3 year cross-sectional research in Dr Sheikh pediatric hospital in Mashhad. Patients with a height less than 5$^{th}$ percentile were evaluated for GHD via insulin stimulation test. Also, thyroid function test was done in all patients. We found 6 (12%) of the children who have a height less than 5$^{th}$ percentile, 5 of whom (83.33% of them or 10% of total) had GHD. There was no statistical correlation between type of disease and GHD (p-value = 0. 667) due to small sample size. Among these 6 patients 4 patients( 66.66%) had ALL. There were 2 (4% of total) cases of subclinical hypothyroidism but with normal height. According to BMI (body mass index), 2 of the patients (4% of total ) were overweight. In our study, ALL patients had an unfavorable height and endocrine side effects. So it seems appropriate to pay more attention to radiotherapy complications in children with cancer, especially ALL to improve their quality of life.*

***Key word**: Growth Hormone Deficiency (GHD) , Acute Lymphoblastic Leukemia (ALL) ,Non-Hodgkin's Lymphoma (NHL),children*

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## INTRODUCTION

Despite of increased 5-years survival of cancers ; malignant neoplasm are still the second leading cause of death (12.8%) in children 1 to 14 years in America [1].. Among these, Acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL) is the most common childhood cancers [2].

According to the great advances in the past 30 years in the treatment and diagnosis of ALL and NHL 5-year survival has increased to 80% , 90% respectively[3]. Most of these children (80%) will suffer from

some complications such as: endocrine disorders (20-50%) including disorders of growth, thyroid function and puberty, changes in Body Mass Index (BMI) and decrease in insulin sensitivity [4, 5]
Most of these disorders happen in adolescence and adulthood, particularly with therapies which have an unfavorable effect on the child's height and growth parameters [6]. After cranial radiotherapy, linear growth velocity decreases during adolescence. In contrast, chemotherapy without cranial radiation therapy induces just a temporary interruption in growth rate, but the final height will be normal [7].
GHD (Growth Hormone Deficiency) is the most common and earliest hormone deficiency in cranial radiotherapy[8].In some studies prevalence of GHD has been reported up to 32% [9]. Recently, by using of focused radiation , potential of neuroendocrin damages has been reduced [10].
Some of endocrinopathies in children with ALL or lymphoma includes primary hypothyroidism, hyperthyroidism, thyroid nodules and goiter [6], Insufficient or delayed puberty and growth are some symptoms of hypothyroidism [5]. These disorders occur in 10 to 15% of patients with leukemia[11].
The aim of this study was to assess the possible growth disorders and GHD in children with ALL and NHL who were under 14 years old at the first of diagnosis.

## MATERIAL AND METHODS

Our study was performed as a cross-sectional study from October 2011 to September 2013 at Dr Sheikh Pediatric Hospital in Mashhad. After the obvious and complete explanation of the aims and process of our study and ethics for the children and their parents, we enrolled 75 patients in our study in the beginning. Nine patients refused to participate in the study. After the initial entrance, seven patients discontinued the process. Unfortunately, four patients died during the study period. Five patients experienced recurrence, and were excluded. Finally 50 children with ALL (n = 25) and NHL (n = 25) were studied in remission phase.
Since the treatment protocols of Non- Hodgkin's lymphoma (including all histological types) are identical with those of acute lymphoblastic leukemia, we ignored treatment details such as dose of radiotherapy and type or amount of drugs used in chemotherapy, in order to avoid confounding statistical factors.
Patients were between 3 to 17 years old and were all first diagnosed before 14 years old. All patients were in complete remission by hematological parameters and bone marrow samples. Chemotherapy and radiotherapy protocols have been adopted in both groups. We excluded the ones with secondary malignancy due to previous treatments. We also omitted those who had chromosomal syndromes such as Bloom syndrome and some congenital disorders like Fanconi anemia. Our patients had not received bone marrow transplantation.
Demographic information such as, gender, age, place of residence were recorded. We measured weight (by SECA Sinker) and height (by stadiometr) in upright position. BMI (Body Mass Index) was calculated using the following formula:
BMI = weight (kg) / height squared ($cm^2$ ).
We evaluated the percentiles of weight and height and BMI of the patients based on standard growth charts. If each child's height percentile for age was under fifth percentile, (s)he would be referred to pediatric endocrinologist to assess for Growth Hormone Deficiency (GHD) by inducing hypoglycemia via insulin stimulation test. We performed this test during a short hospitalization period under strict supervision of a pediatrician and an expert nurse. The amount of insulin administered to those younger than 5 years was 0.05 u/kg (unit per kilogram of body weight) and for those older than 5 years was 0.1 u/kg. We used regular insulin intravenously that was diluted with a little amount of distilled water. At the beginning of testing and before insulin injections fasting blood sugar (FBS) was checked at zero minutes. If the value of this sample was less than 60 mg / dl, we discontinued this test. In addition to a thorough workup for growth hormone status, we also evaluated hypopituitarism by drawing 10 cc blood sample as clot to measure serum levels of Growth Hormone (GH ), insulin growth factor -1 ( IGF-1 ), insulin growth factor binding protein – 3 ( IGFBP3), adrenocorticotropin hormone ( ACTH ), cortisol and prolactin (PRL). So we accessed an intravenous line and then at 15, 30, 45 and 60 minutes after the injection of insulin, 2 ml venous blood samples were taken for the measurement of serum GH, blood sugar (BS). The samples were sent to the endocrinology laboratory regarding cold condition to transport sample. If the increase in GH levels were less than 10 nanogram per deciliter (ng / dl) in all samples during successive sampling, the case would be made for growth hormone deficiency (GHD).On the other hand, to better workup for short stature and also pituitary-hypothalamus axis, we studied serum levels of TSH (thyroid stimulating hormone) and T4 (thyroxin hormone) to evaluate probable thyroid dysfunction in all our patients.
We performed t-test for variables with normal distribution, and Mann - Whitney test for non-normally distributed variables . For qualitative variables (name and rank) in both groups, cross - tab (Fisher's exact and chi– square test) were used. We considered p value ≤ 0.05 as statistically significant differences.

The sample size was calculated based on the study by Benmiloud in 2010 [6] according to the following formula:

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 (s_1^2 + s_2^2)}{(\bar{x}_1 - \bar{x}_2)^2}$$

Therefore, we got at least 10 people in each group. To strengthen the power of our study, we increased the sample size to of 25 cases in each group to prevent sample decline. Sampling method was non-probability, simple and purposeful. We collected data experimentally using a checklist**.**

**RESULTS**

We found 6 children with height less than fifth percentile who were referred to pediatric endocrinologist.
**By sex** ; 48 % of patients with ALL , 60% of patients with NHL were male (P-value = 0.569). Among the 6 patients with a height less than the 5th percentile, one was female and five were male. (P-value = 0. 211)
**By age**: Our results in evaluating of percentiles of growth parameters for age and sex were showed in table I.

Table I - percentiles of growth parameters for age and sex in all patients.

| **Percentile for age & sex** | < 5% | 5-95% | >95% |
|---|---|---|---|
| **height** | 6(12%) | 43(86%) | 1(2%) |
| **weight** | 6(12%) | 41(82%) | 3(6%) |
| **BMI** | 4(8%) | 41(82%) | 5(10%) |

By WHO qualities definition for BMI, 48 patients (96% of all) had a normal BMI, and 2 patients (4% of total) were overweight.
**By Puberty**; the maturation stage (tanner stage) in all patients was normal for their age and none of them had precocious puberty or delayed puberty, even those who had GHD.
Due to confounding effect of age on weight, height and BMI, we used regression test (by removing the confounding effect of age) plus T-test and the following results were found:
**A)** There was a significant difference in height average between the two groups of ALL and NHL ( p value = 0.007, p- value = 0.003 respectively) .
**B)** There was no significant difference in weight and BMI average between the two groups of ALL and NHL ( p value = 0.060 for weight, p- value= 0.179 for BMI).
We found 6 (12% of total) children were under 5th percentile of height for age and sex. 4 of them (8%) had ALL and 2ones (4%) had NHL(See Table II) . There was no significant difference in average height between the two groups of ALL and NHL (p-value= 0.667) among these 6 patients, possibly due to the limited number of cases.

**Table- II: Distribution of patients according to type of disease and height percentile**

| **Type of disease / Height Percentile** | **ALL (%)n** | **NHL (%)n** | **Total (%)n** |
|---|---|---|---|
| **Lee than 5th percentile** | 4( 8%) | 2(4%) | **6(12%)** |
| **More than 5th percentile** | 21(42%) | 23(46%) | **44(88%)** |
| **Total** | 25(50%) | 25(50%) | **50(100%)** |
| **Fisher's exact test result** | **0.667=P-value** | | |

ALL: Acute Lymphoblastic Leukemia , NHL: Non-Hodgkin's Lymphoma (NHL)

We found 6 patients (12% of total) with short stature (less than 5th percentile of height),So we evaluated GHD (Growth Hormone Deficiency), via insulin stimulation test on theses 6 children. Five of six patients (83.33%, 10% of total) had GHD, as the serum level of GH did not increase more than 10 ng/dl.
Furthermore also we measured the serum level of other pituitary hormones to evaluate panhypopitutarism in these 6 patients. Our results showed normal values for Cortisol, ACTH, prolactin, IGF-1 and IGF-BP3. Therefore, none of these 6 patients had panhypopitutarism and 5 children among them had isolated GHD.

We referred to their previous admission files and monitored the weight and height of patients, and found that only 2 of these 6 patients had height and weight less than 5th percentile at the time of diagnosis and before any treatment. The other patients' (4 of 6) weight and height of the others (4of 6 patients) were more than the 50th percentile.

According to thyroid study,there was no significant difference in mean TSH and T4 between the two groups of ALL and NHL patients ( TSH: p- value= 0.567 , T4: p- value= 0.567 ). It is notable that the clinical data were individually matched based on age for every patient.

We found subclinical hypothyroidism in 2 boys with ALL (6 and 14 years old) .Both of them were referred to pediatric endocrinologist for more workup. It was interesting that none of them had GHD and both of them had normal growth parameters. The 6 patients with height less than 5th percentile had normal thyroid function.

**DISCUSSION AND CONCLUSION**

Leukemic children who have had cranial or craniospinal radiation are at high risk for GHD. However, chemotherapy alone in ALL children can also lead to short stature[12].

The following factors may increase the risk of GHD:1) Fractional TBI compared to single-dose radiation .2) Cranial radiotherapy before a bone marrow transplant .3) Female sex 4) Effects of treatment, such as GVHD (Graft versus host disease) .5) Bosulfan and cyclophosphamide-containing regimens [13].GHD in adolescence can lead to a decrease in Lean Body Mass, obesity and osteopenia. However, hypothyroidism should also be considered in short stature[14].

This cross-sectional study was performed for the first time in Dr. Sheikh Pediatric hospital in Mashhad. We studied 50 children with ALL (n= 25) and NHL (n = 25) who were in remission phase. Patients were at 3 to 17 years old and the age at diagnosis in all of them was under 14 years. Six of these children (12% of total) were located under 5th percentile chart of height for age and sex. Four of them (66.66%) had ALL and two (4% of total) had NHL. According to insulin stimulation test, five children had isolated GHD and none of these 6 patients had panhypopitutarism. Only 2 of the 6 patients had height and weight less than 5th percentile at the beginning of diagnosis and before any treatment. The other 4 patients had a weight and height more than 50th percentile at the beginning. So it seems that ALL itself may pose a higher risk for side effects such as GHD (compared to NHL).

Duffner, et al demonstrated that radiotherapy or even just chemotherapy (high-dose metotroxate) in children with ALL had led to some complications such as hypothyroidism and GHD as the common endocrinopathy. They reported younger age, higher doses of cranial radiation as risk factors[15].

Eric-J Chow and his colleagues evaluated adult patients' height who have had had childhood ALL During a 5-year prospective study of 2434 cases of ALL. Compared with their siblings, these patients were shorter {more than 2 SD} (P <0.001). Related risk factors for short stature in their study included:

ALL diagnosed before puberty, higher doses of cranial radiation (equal to or greater than 20 Gy), any radiation to the spine, and female sex. Patients with cranial or spinal radiation earlier in life had lower height in this study[16].In our study, there was a significant difference in mean height between ALL and NHL patients (p value = 0.007).

In Eric-J Chow s study female sex was a risk factors , in our study, oppositely there was no significant relationship between height and gender (p = 0.211)

Theresa Haddy studied height of 347 ALL patients. If a patient's height was less than 5th percentile, they evaluated growth hormone by arginine or clonidine stimulation test. Among 112 ALL survivors GHD was confirmed in 5 patients [7].

In our study on 50 children with ALL,NHL, six patients had a height less than 5th percentile who were evaluated by insulin stimulation test. Our results showed that 5 children (10% of total) had GHD. Insulin stimulation test may lead to hypoglycemia but has more definitive results even in one time compared with arginine and clonidine stimulation tests. In order to less harm and cost we evaluated them by one short-term hospitalization under strict supervision.

Skaler and colleagues mentioned that although assessment of IGf-1 and IGfBP3 are used in GHD approaching, these parameters are not reliable indicators for those who have had cranial radiotherapy. So when GHD is confirmed by stimulation test, IGf-1 and IGfBP3 may be still in the normal range [4]. Values of IGf-1 and IGfBP3 were normal in our children with GHD, although the insulin stimulation test had confirmed the GHD diagnosis.

Peak pubertal growth velocity and premature puberty have a positive correlation with age and treatment [17]. Cancer treatment, especially in children with GHD effects on the maturation process [18,19]. We investigated the maturation stage according to tanner stage. None of our patients had precocious puberty or delayed puberty, even the ones who had GHD.

Research Center CCSS (Childhood cancer survivor study) reported that in individuals with childhood ALL, there is no relationship between chemotherapy alone and risk for obesity or BMI changes. But these patients are at a higher risk for visceral obesity and increased body fatness despite normal BMI [20, 21].Children with ALL who have received only chemotherapy may also have increased BMI z-scores at the end of treatment [22].

In our study, by WHO qualities definition for BMI, 48 patients (96% of total) had a normal BMI, and 2 patients (4% of total) were overweight, one of whom was a 17 year old boy with ALL and the other one was a 17 year old boy with lymphoma. Furthermore, in our study, 6 patients (12%) were less than or equal to 5th of weight percentile. In 41 patients (82%) weight was between 5th and 95th percentiles and in 3 children (6 %) it was higher than 95th percentile.

Sklar, et al noted that hypothyroidism occur within 2 to 5 years after cancer treatment [23], whereas in our study hypothyroidism almost occurs immediately after the primary treatment .The whole process of our study lasted 3 years. Therefore, perhaps if we were following thyroid function longer, we would obtain different results.

Our study was the first attempt to evaluate endocrine complications in the pediatric oncology ward at Dr. Sheikh pediatric hospital in Mashhad, so some basic data were not available. In order to obtain a statistically valid assessment, we had to omit some variables in our study. Furthermore, some patients refused to participate or continue our study and a few of our patients died, leading our study population to drop to 50.We had also some financial limitations. According to variety of factors affecting growth velocity from birth to full maturity, to avoid statistical confounding factors, we investigated only a certain number of factors. It seems necessary to do similar studies with a larger study population and longer follow up in the future.

We suggest that it is better to collect patient information including height, weight, BMI at the time of diagnosis and then at regular intervals during treatment and in long-term follow-ups after treatment. Secondly observe these parameters carefully and refer them to a pediatric endocrinologist if any abnormality is detected. Furthermore note to growth hormone and thyroid disorders if there is abnormal growth velocity .

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**Abbreviations**

ALL: Acute Lymphoblastic Leukemia; NHL: Non-Hodgkin's Lymphoma (NHL); BMI: Body Mass Index; GHD: Growth Hormone Deficiency ;WHO: World Health Organization; SD: Standard Deviation; MRI: Magnetic Resonance Imaging ; FSH : Follicle-Stimulating Hormone; LH : luteinizing Hormone.; GH: Growth Hormone ; IGF-1 : Insulin Growth Factor -1 ; IGFBP3 : Insulin Growth Factor Binding Protein – 3 ; ACTH: Adrenocorticotropin Hormone ; PRL : Prolactin; TSH : Thyroid Stimulating Hormone; T4 : Thyroxin hormone; FBS: Fasting Blood Sugar; BS: Blood Sugar; HSCT : hematopoietic stem cell transplantation; TBI :total body irradiation; GVHD :Graft versus host disease

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