

Radiation-induced hypopituitarism in children with acute lymphoblastic leukemia

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ABSTRACT

Background: Acute Lymphoblastic Leukemia (ALL) is the most common malignancy among children for whom radiotherapy and chemotherapy are used for treatment. When hypothalamus-pituitary axis is exposed to radiotherapy, children's hormone level and quality of life are influenced. The aim of this study is to determine late effects of radiotherapy on hormonal level in these patients. **Materials and Methods:** In this study 27 children with ALL, who have been referred to Shahid Ramezanzadeh Radiation Oncology Center in Yazd-Iran and received 18-24 Gy whole brain radiation with Cobalt 60 or 9 MV linear accelerator, were assessed. These patient's basic weight, height and hormonal levels were measured before radiotherapy and also after different periods of time. **Results:** GHD (growth hormone deficiency) after clonidine stimulation test was observed in 44% ($n=12$) and that in 50% of them ($n=6$), less than 1 year, had been passed from their radiation therapy. None of these patients demonstrated hormone deficiency in other axes. **Conclusions:** This study showed that even application of a 18-24 Gy radiation dose might influence growth hormone levels; therefore, we recommend reduction of radiotherapy dose in such patients whenever possible.

Key words: Acute lymphoblastic leukemia, hypopituitarism, radiation

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most current malignancy among children, which has at least 75% long-term survival.^[1] These patient's treatment protocols are different in amount of prescription of chemotherapy drugs and radiotherapy.^[2]

Neuro-endocrine abnormalities may occur after external cranial radiotherapy in most of the brain tumors and hematologic malignancies when hypothalamus-pituitary axis is exposed to radiotherapy.^[3] Deficiency of one or two hormones of anterior pituitary have been described after cranial radiotherapy for primary brain tumor, tumors which impact hypothalamus-pituitary axis (HPA), nasopharyngeal tumors, skull base tumors and solid tumors in the head and neck. These conditions have been reported after cranial prophylactic radiotherapy has been used for treatment of children with ALL and before whole body radiation precise bone marrow

transplant.^[4] Since the rate of cancer incidence is rising continuously, it is expected that in the four future decades there will be many survivors predisposed to developing endocrine complications. Often, these patients do not undergo routine treatment of endocrine complications when required. However, appropriate treatment and management of RIH provides an important tool for attainment outcomes and upgrading the quality of life (QOL) in these patients.^[5]

Pituitary and hypothalamus function of children and adults specifically is sensitive to head and neck radiotherapy.^[6] Radiation terminating to neurotoxicity (and related to hypothalamus-pituitary axis) depends on total dose of radiation, fraction size and the time interval between fractions giving opportunity to tissue repairing.^[7] Usually the next manifestation of hypopituitarism indicates damage of hypothalamus towards atrophy of radiated pituitary cells.^[6] Mechanisms specifically developing patterns of RIH incidence, GHD and gonadotropin deficiency that occur more commonly and usually earlier than corticotroph and thyrotroph insufficiency are unknown. The thyrotroph and corticotroph axes are known to be less sensitive to radiotherapy. Diabetes insipidus are not considered as a result of radiotherapy. Even though in 61% of patients usual manifestations of pituitary failure include GHD, gonadotrophins, ACTH and finally TSH deficiency; however, RIH can

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assume any temporal sequence of hormonal deficiencies. Routine tests for examination of pituitary hormones axis is required.^[8] Anterior pituitary hormone deficiencies are the most common complication of successful cancer treatment in children and adults. However, these deficiencies have undesirable effects on growth, body image and composition, sexual function, skeletal health and quality of life.^[4]

As ALL is the most common cancer among children and has relatively high rate of survival, the aim of this study is in determining radiotherapy complications in these children after a period of time is spent on their radiation treatment.

MATERIALS AND METHODS

Anterior pituitary hormone deficiencies were examined in 27 children with ALL referred to Shahid Sadoughi Hospital, Yazd-Iran. These children had received whole brain prophylactic or therapeutic radiotherapy as part of their treatment. Radiotherapy had been performed using Cobalt60 machine or linear accelerator (LINAC) with two-dimensional method. Total dose was 18 Gy in prophylactic setting and 24 Gy in CNS involvement or CNS recurrent cases using 1.8-2 Gy daily fraction size and 5 fractions weekly. In these patients in the first visit and before treatment their weight and height were assessed. Before treatment and during different later periods, patients were examined for anterior pituitary hormones with clonidine stimulation test and for measuring their growth hormone level and other hormones such as TSH, T₃, T₄, prolactin, estradiol, ACTH and also FSH, LH and testosterone (when required). Also their height and weight in the time of testing hormones were reassessed.

The protocol for the time periods of tests was as following:

- First test: before radiation
- Second test: 6 months after radiotherapy and other tests: every year.

Static analysis was performed with SPSS 17 software.

RESULTS

Seventy percent of patients were male and 30% female. Average age of the patients was 5.5 years. Weight, height and serum hormonal levels were measured in different times (from 2 months to 9 years) post radiotherapy and these results were obtained: Growth hormone deficiency (GHD) following clonidine stimulation test was observed in 44% ($n=12$) in 50% of whom ($n=6$) it was less than 1 year after radiotherapy.

From all of cases, 5 persons received 24 Gy (therapeutic dose) and 22 persons received 18 Gy (prophylactic dose). GHD was observed in 100% of patients with therapeutic protocol and 31.8% of patients with prophylactic therapy.

None of these patients demonstrated thyrotroph axis deficiency and only in 2 of them TSH level was more than 5 ng/dl. ACTH and cortisol axes even after 9 years follow-up were normal. Children in pubertal age were tested for sexual hormones which showed normal results. In 18.5% ($n=5$) of participants, obesity (or overweight) was seen.

DISCUSSION

This study like most other studies did not use radiation protocols more than 2 Gy per fraction and more than 5 fractions per week. Increasing fractions size more than 2 Gy in each fraction (for the same total dose) can relatively result to more damages to the nervous system.

As it was mentioned, in this study 44% of patients had deficiency only in growth hormone axis and in half of them less than 1 year had passed from radiotherapy. In certain studies it has been pointed out that hypopituitarism occur mostly in the first decade following radiotherapy in patients than whose pituitary has been exposed to radiation, and in more than 80% somatotroph, gonadotroph, thyrotroph or corticotroph deficiency occurs.^[6] In the time of appearance of hypopituitarism, morbidity rate in survivors is duplicated.^[9] Clinical consequences of radiation protocols in patients are different according to age and sex. In childhood, RIH can disturb somatic, mental and sexual development with declined growth hormone, secretion of thyrotroph hormone and disruption of pubertal time process. It has been reported that somatotroph hormone axis in children is more sensitive to radiation than adults. In one research, 59% of childhood cancer survivors who received whole brain radiotherapy with dose of 18 Gy for hematologic malignancies demonstrated blunted responses to stimulation test of growth hormone,^[10] which was more than twice frequency of GHD in adults with same radiation dose.^[11] In our study, this rate was about 44%. This difference can be explained regarding children's more need to growth hormone and factors making their somatotrophic cells more sensitive to radiation. Although more studies indicate that incidence of RIH is more common and possible during first 5 years after exposure to radiation, new deficiencies which have not existed before can occur after 20 years in survivors.^[8,12]

In this study we used clonidine stimulation test for GHD diagnosis. Researches represented that GHD diagnosis in patients exposed to radiation should be examined according

to decrease in level of Insulin-like Growth Factor I (IGF-I) in patients with multi-hormonal deficiencies of pituitary or structural abnormality of pituitary, which has 96% accuracy in prediction of GHD.^[13] However, in one other study, 31-60% of patients with GHD had IGF-I normal rate; therefore, another stimulation test for GHD diagnosis is required.^[14] Insulin tolerance test (ITT) is considered as gold standard for diagnosis of GHD in cohort studies at radiotherapy field.^[15]

In some of patients obesity was seen. All patients with systematic malignancies and brain tumors are highly at risk of some degrees of obesity because of various mechanisms.^[16-19] These patients need follow-up for assessing endocrine hormones and replacement hormone therapy if required.^[10]

As a result of this study, we counsel our protocol for follow-up of children who had received cranial irradiation: check for pituitary and hypothalamus function tests, especially GH and thyroid functional tests every 6-12 months in first 5 years after cranial radiation therapy and check for same hormonal tests every year in the second 5 years.

More follow-up studies are recommended to find a possible safe radiation dose hormone replacement to increase quality of life of patients. Limitations of this study were impossibility of more accurate follow-up.

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