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# Central Hypothyroidism: A Rare Complication in a Child Undergoing Chemotherapy for Acute Lymphoblastic Leukemia

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## Abstract

Abnormalities of the thyroid gland are among the most frequent endocrine complications observed in childhood cancer survivors. We report an 11 years old girl who developed central hypothyroidism and ACTH deficiency during the chemotherapy for CNS relapse of acute lymphoblastic leukemia before receiving radiotherapy.

**Keywords:** Thyroid gland, hypothyroidism, chemotherapy, acute lymphoblastic leukemia.

## Introduction

Pediatric patients with acute lymphoblastic leukemia (ALL) can experience endocrine dysfunction during therapy, after therapy, and even many years later which can cause significant morbidity and mortality [1]. Abnormalities of the thyroid gland are among the most frequent endocrine complications observed among childhood cancer survivors [2]. Untreated hypothyroidism in childhood and adolescence may cause neuropsychological symptoms such as chronic tiredness, mental fatigue, and learning difficulties, so the early recognition and treatment of thyroid dysfunction seems to be crucial in this population [3].

Whilst the effects of direct and indirect radiotherapy on thyroid function are indisputable and have been confirmed by several studies [4-6], there are only a few studies documenting the effects of chemotherapy. We report an 11 years old girl who developed central hypothyroidism and ACTH deficiency during the chemotherapy for CNS relapse of acute lymphoblastic leukemia before receiving radiotherapy.

## Report of the Case

An 11-year-old girl was diagnosed with acute lymphoblastic leukemia at our hospital (ALL, IC 2002 protocol, intermediate risk group). Routine imaging examinations before treatment introduction (brain magnetic resonance imaging, abdominal ultrasound scan as well as neck and thyroid ultrasound scan) showed no abnormalities. She received induction, consolidation, and continuation chemotherapy based on BFM-ALL-2002 protocol without delay. Six months after diagnosis, she was found to have leukemic blasts in her CSF without any clinical symptoms. Brain MRI was repeated and was found to be normal. CNS relapse protocol was started with concomitant triple intrathecal chemotherapy until the CSF became clear.

After discontinuation of dexamethasone which was started as reinduction chemotherapy, she presented with inconsistent obesity and fatigue. A pediatric endocrinologist was consulted, and endocrine tests were requested. The results are shown in table 1.

Thyroid function tests were consistent with central hypothyroidism. There was also ACTH deficiency resulting from chronic suppression due to the prolonged use of pharmacologic doses of glucocorticoids. Brain MRI was done for the third time and it was still normal. Levothyroxine and hydrocortisone were administered and fatigue disappeared after a week and her obesity was decreased after one month.

**Table 1:** Patient's Laboratory Data.

| Tests | Patient's results | Reference range |
|---|---|---|
| FBS | 84 mg/dl | 70-115 |
| Triglycerides | 103 mg/dl | <200 |
| Cholesterol | 148 mg/dl | <200 |
| Calcium | 9.2 mg/dl | 8.6-10.2 |
| Phosphorus | 4.9 mg/dl | 4-7 |
| SGOT | 31 U/L | 0-40 |
| SGPT | 34 U/L | 0-50 |
| Vitamin D (25OH) | 10 ng/ml | >30 |
| T4 (ECL) | 4 micg/dl | 5.7-14 |
| T4 Uptake (ECL) | 0.8 TBI | 0.83-1.13 |
| FTI | 5 ug/dl | 4.9-16.7 |
| TSH (ECL) | 0.3 micIU/ml | 0.66-4.14 |
| Cortisol (ECL) | 12.5 nmol/L (0.45 micg/dl) | 171-536 |
| ACTH (8AM) | <0.2 | |

# Discussion

Thyroid dysfunction has been reported during remission induction therapy for childhood ALL [7] and as a late complication in patients who receive cranial irradiation [8, 9]. Whilst the effects of direct and indirect radiotherapy on thyroid function are indisputable and have been confirmed by several studies [4-6], there are only a few articles documenting the effects of chemotherapy. Moreover, the existing studies have yielded contradictory results. Some studies have included chemotherapy, addressing it as a possible additional risk in patients receiving radiotherapy [10-12] , while few have focused on the thyroid toxicity of chemotherapy alone [13,14].

The effect of chemotherapy alone on thyroid function has been examined by Nygaard et al. [9] in 61 children who were off therapy for a median of 25 months (range, 2 months to 10.3 years). None of the patients examined showed clinical signs of hypothyroidism or hyperthyroidism, and serum T4, free T4, TSH, and T3 uptake values did not differ from those of controls. Similarly, 57 of the 95 patients evaluated by Lando et al. [13], 1.2-18.3 years after completion of ALL therapy had normal hormone levels and a normal TSH response to TRH stimulation. Chemotherapy was also not found to pose an additional negative effect on the function of the HPTA in investigations by van Santen et al., [10] or Schmiegelow et al.,[11]. In a more generalized study reported by Rose et al., chemotherapy was found to be associated with an increased risk of hormonal deficiency, which was defined as one of the triad of growth hormone deficiency, hypothyroidism or pubertal abnormality [14].

In central hypothyroidism, FT4 declines because of impaired hypothalamic-pituitary release of TSH. FT4 and T4 values are similar to those seen in mild primary hypothyroidism. However, the ability to increase TSH secretion is impaired, so the 'red flag'

of an elevated TSH concentration is absent. The signs and symptoms of hypofunction of the thyroid gland are non-specific [13].

Symptoms of central hypothyroidism (e.g. asthenia, edema, drowsiness, adynamia, skin dryness) might be of gradual onset and can go unrecognized until treatment is begun and the patient subsequently feels better [15, 16].

On the other hand, apart from transient ACTH deficiency resulting from chronic suppression due to the prolonged use of pharmacologic doses of glucocorticoids, ACTH deficiency in childhood cancer survivors is relatively uncommon. It can be observed either as a result of direct tumoral impingement on the hypothalamic-pituitary axis and surgery in that region, or following high-dose (O30 Gy) radiation [14, 15, 17]. In a study on children receiving treatment for CNS embryonal tumors that included high doses of radiation to the hypothalamic-pituitary area (median dose 44 Gy), the 4-year cumulative incidence of ACTH deficiency was 38% [18]. As different investigators use different methods to establish a diagnosis of ACTH deficiency, comparison between studies can be difficult.

## Conclusion

Awareness of the potential for the development of subtle endocrine alterations among patients undergoing chemotherapy for acute lymphoblastic leukemia might permit the development of treatment methods that reduce the frequency of endocrine deficiencies.

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