

Cranial Irradiation and Central Hypothyroidism

Survivors of therapy for tumor infiltration of various sorts in the hypothalamic-pituitary area frequently have tropic hormone deficiencies. These deficiencies are known as central hormone deficiencies and produce "secondary" hormone deficiencies of the peripheral endocrine glands (thyroid, adrenal, gonads). Destruction of these peripheral glands directly results in primary thyroid, adrenal, and/or gonadal deficiency. Patients receiving irradiation of the head often end up with either primary or secondary thyroid deficiency—or both—because the thyroid and pituitary glands both receive irradiation as a result of the proximity of the thyroid gland to the hypothalamic-pituitary area. Rose reviews in this article the effects of cranial irradiation on regulatory cells of the pituitary gland. She then summarizes the characteristics of mild hypothyroidism (primary, central, and mixed) resulting from radiation therapy, discusses diagnostic methods, and recommends guidelines for the treatment of central hypothyroidism.

Rose's review is too extensive to abstract for *GROWTH, Genetics & Hormones*, but its thoroughness and importance must be brought to the attention of any physician working with children or adults who have received intracranial irradiation. Early in the article the effect of different types and doses of radiation upon various physiologic parameters is covered. The following section pertains to regulation of the thyroid axis and emphasizes the circadian pattern of thyrotropin secretion and how measurement of the normalcy or abnormalcy of this parameter is helpful in differentiating central, primary, and mixed hypothyroidism. The third section discusses primary hypothyroidism resulting from mantle irradiation for Hodgkin's disease,

cranial irradiation for medulloblastoma, and total body irradiation in preparation for bone marrow transplant. Dr. Rose emphasizes that primary hypothyroidism is very frequently associated with secondary hypothyroidism in these instances. Central or secondary hypothyroidism then is considered; emphasis is placed on the frequent occurrence of free thyroxine (T_4) levels in the low normal range and on the absence of elevated thyrotropin levels. A blunted or absent nocturnal thyrotropin surge is a characteristic of central hypothyroidism, suggesting loss of the normal circadian variation in thyrotropin-releasing hormone (TRH) release. Mild hypothyroidism, both central and primary as well as mixed, is considered. Dr. Rose urges treatment for all patients with mild hypothyroidism, whether primary or secondary. "Even mild TSH (thyrotropin) rises might be a sign of possible thyroid dysfunction and should not be ignored." The opportunity to improve growth rate will be missed."

A subsequent section considers *mixed hypothyroidism*, which is a newly named syndrome consisting of central hypothyroidism associated with elevated thyrotropin. Secretory dynamics are abnormal.

A subsequent section deals with treatment of central hypothyroidism. One recommendation is that T_4 therapy in patients with central hypothyroidism should be adjusted to keep the free T_4 values at 1.4 to 1.6 ng/dL.

Dr. Rose observes that the cause of poor growth in childhood cancer survivors cannot always be identified. Although often caused by toxic effects of chemotherapy, radiation effects on bone growth centers, or GH deficiency, poor growth also can in many cases be caused by undiagnosed central hypothyroidism. Central hypothyroidism is much more common after radiation therapy for childhood cancer than has generally been recognized. Early identification and treatment of hypothyroidism can improve the quality of life and optimize the final adult height of these patients.

Rose SR. *Trends in Endocrinol & Metab* 2001;12(3):97-104.

Editor's comment: *The use of free T_4 screening and of confirmatory testing that combines the thyrotropin surge test with the TRH test should improve the sensitivity with which central hypothyroidism is diagnosed. The thyrotropin surge and TRH tests should be used to assess thyroid status in cancer survivors whose free T_4 value is in the lowest third of the normal range, whose basal thyrotropin concentration is normal, and whose growth rate is slowed. Other hypothalamic-pituitary axes should be evaluated concurrently as clinically indicated. Much improvement in diagnosing and treating primary, secondary, and tertiary hypothyroidism has occurred in the last 10 years. Dr. Rose's article is an excellent summary of these advances and how to apply them.*

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