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# A review of radiotherapy-induced hypopituitarism

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*Radiotherapy is integral to the treatment of pediatric and adult brain, endocrine, and nasopharyngeal tumors, but can induce late endocrine system effects such as hypopituitarism, with potentially profound implications for survivors' growth, sleep cycle, sexual functioning, osteoporosis risk, and quality of life. Nurses play key roles in assessing and educating patients, and devising and communicating long-term posttreatment patient care and surveillance plans. This column reviews the risks, detection, and management of radiotherapy-induced hypopituitarism.*

With new anticancer treatments, such as checkpoint-blockade immunotherapies, novel patterns of late neuroendocrine system dysfunctions, known as endocrinopathies, are emerging among patients with cancer.[1] Longstanding patterns of radiation-induced hypopituitarism (RIH) and other endocrinopathies among survivors who have undergone radiotherapy for brain and nasopharyngeal (head-and-neck) tumors might also change with better dose-targeting modalities like intensity-modulated radiotherapy (IMRT) and radiosurgery, which spare healthy tissues.[2-7] However, even with IMRT, endocrine organs will still sometimes be exposed to radiation fields.

"IMRT for tumors away from the H-P axis is not expected to result in pituitary dysfunction, as the H-P axis will be spared from irradiation," explains Ken H. Darzy, MD, FRCP, MBChB, of Queen Elizabeth II Hospital in Welwyn Garden City, Hertfordshire, United Kingdom. "However, with nearby tumors it may not be possible to spare the H-P axis completely and a degree of pituitary dysfunction may be expected."

RIH will also continue to be a risk faced by patients treated for pediatric and adult endocrine system neoplasms, such as pituitary adenomas, or prophylactic whole-body or whole-brain irradiation.[3,8-10] One recent study found that gamma knife stereotactic radiosurgery for pituitary adenomas yielded superior radiation sparing of hypothalamus tissue compared with IMRT and Linac-based 3D-conformal radiotherapy (CRT), with resulting lower rates of early RIH; 12.5% of patients who underwent radiosurgery experienced one or more hormone deficits after irradiation, compared with 72% of patients who underwent CRT and 50% of patients who received IMRT.[7] (A previous study found a long-term new hypopituitarism rate of 30% among patients undergoing stereotactic radiosurgery for pituitary adenomas, after a followup period of up to 150 months.[11]) Sparing hypothalamus tissue from irradiation was once thought to reduce RIH risk but that no longer appears to be the case.[3]

Nevertheless, the irradiation of neuroendocrine organs is commonly not considered in radiotherapy planning, and nasopharyngeal cancer treatment guidelines do not specify hypopituitarism as a long-term adverse event following radiotherapy.[2] Oncology nurses should be familiar with RIH. Nurses are often responsible for creating late effects treatment summaries, and care and surveillance plans, and communicating risks and plans to patients and pediatric patients' caregivers or guardians.[12] Because of the occurrence of secondary cancers among adult survivors of childhood cancers, oncology nurses are likely to encounter patients in oncology settings who have RIH stemming from treatment during childhood or adolescence. With longer survival times among patients treated for cancer, and a consequently increasing prevalence of patients with late endocrinopathies, nurses and cancer center managers have identified a need to improve nurses' expertise in endocrine late effects of cancer treatment.[13]

> RIH effects are more pronounced among people treated as children and adolescents than during adulthood.

## Hormones affected by RIH include growth hormone, gonadotropin, ACTH, prolactin, and TSH.

RIH is irreversible and progressive, causing impaired production of key hormones and resulting in growth disruption, circadian and sleep disturbances, sexual side effects, elevated risk of osteoporosis and obesity, and reduced quality of life.[3] Onset can occur soon after radiotherapy ends or years later.

The pituitary gland secretes several hormones, which interact in sometimes complex ways with other endocrine glands, such as the adrenal and thyroid glands, and the ovaries and testicles. RIH-associated pituitary hormone deficiencies can cause downstream target organ deficiencies in the secretion of cortisol, thyroxine, estrogen, and testosterone, with numerous resulting signs and symptoms (See Signs, symptoms, and associations of hypopituitarism).

Generally, RIH effects are more pronounced among people treated as children and adolescents than during adulthood; for example, RIH-associated growth hormone deficits can impair a child's eventual adult height or stature. Up to 41% of all survivors of childhood cancers, and nearly all children who received radiation doses greater than 30 Gy, experience endocrinopathies, of which RIH-associated growth hormone deficiency is the most common form.[2] The risk of RIH appears to climb during the decade following irradiation of endocrine organs, making long-term surveillance important in timely diagnosis and clinical intervention.[2,3]

Overall, a recent meta-analysis of data from 18 studies concluded that RIH occurs to some degree in 66% of adult patients whose hypothalamus or pituitary glands were included in cranial radiotherapy fields for non-pituitary (brain or nasopharyngeal) tumors; growth hormone deficiency prevalence was 45%.[4]

"The onset and severity of radiation-induced hypopituitarism primarily depends on the total radiation dose, the fraction size, and the time allowed between fractions for tissue repair (ie, duration of the radiation schedule)," notes Darzy.[9] Larger radiation dose fractions "inflict more damage on the H-P axis than do schedules administered over a long duration" with smaller fraction doses.

Generally, radiation doses less than 40 Gy are associated with isolated RIH-associated deficiencies in growth hormone or gonadotropin (the second most common manifestation of RIH).[3] Intensive radiotherapy doses exceeding 50 to 60 Gy can cause deficiencies in multiple other hormones as well, including adrenocorticotropic hormone (ACTH), in up to 60% of patients at 10 years postradiation.[3,9] ACTH deficiencies can trigger hypoadrenalism and cortisol deficiency, which can cause fatigue, muscle weakness, nausea, dizziness, weight loss, and hypoglycemia.[12] In prepubertal children, and particularly girls, even radiation doses less than 25 Gy can increase the risk of precocious puberty.[2]

Prolactin and TSH hormone levels can be assessed using blood tests, as indicated by signs and symptoms of RIH, and treated with dopamine agonists such as cabergoline and L-thyroxine replacement therapy, respectively.[2] Gonadotropin dysfunction is inferred by low serum

### Signs, symptoms, and associations of hypopituitarism

The healthy anterior pituitary gland secretes several hormones:

- Growth hormone (GH)
- Adrenocorticotropic hormone (ACTH)
- Thyrotropin (TSH)
- Luteinizing hormone (LH)
- Follicle-stimulating hormone (FSH)
- Prolactin
- Gonadotropin

Depending on which of these are affected by radiotherapy-induced pituitary dysfunction, symptoms can vary. Onset of symptoms can be gradual. Symptoms are nonspecific and may be subclinical, and go undiagnosed for several years. Symptoms include:

- Fatigue
- Weight changes (weight loss or increased fat mass and reduced lean body mass)
- Decreased appetite
- Decreased sex drive and sexual function
- Infertility
- Changes in menstrual cycles or lactation in breastfeeding women
- Hot flashes
- Hair loss
- Sensitivity to cold
- Difficulty staying warm
- Sleep disturbances
- Cardiovascular disease
- Impaired skeletal growth (height or stature) during childhood and adolescence

**SOURCES**

Darzy KH. Radiation-induced hypopituitarism. *Curr Opin Endocrinol Diabetes Obes.* 2013;20(4):342-353; Hypopituitarism: symptoms. Mayo Clinic Web site. http://www.mayoclinic.org/diseases-conditions/hypopituitarism/basics/symptoms/con-20019292. Accessed July 17, 2014.

testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) in males, and low FSH, LH, and estradiol in women on menstrual cycle day 2, or simply low FSH and LH among postmenopausal women.[2] In children, growth hormone–releasing hormone analog therapy can correct gonadotropin deficiencies.[2]

## SURVEILLANCE AND FOLLOW-UP

The hormones affected by RIH include growth hormone, and less frequently, gonadotropin, ACTH, prolactin, and thyroid-stimulating hormone (TSH).[2] Because the risk and severity of radiation-induced endocrinopathies increase over time after radiotherapy, posttreatment plans should include long-term monitoring for hypopituitarism for children and adolescents, to ensure timely detection and intervention with hormone replacement therapies.[3,9] For adult cancer survivors, testing is undertaken only if signs and symptoms of endocrinopathy emerge.

A normal ITT result 10 years after radiation exposure usually eliminates the need for further annual testing.

The Insulin Tolerance Test (ITT) is considered a gold standard for identifying RIH growth hormone deficiency.[3] "A failed response to the ITT in cranially-irradiated patients is accepted as diagnostic of GH deficiency without the need to resort to further tests," he notes.[9] (Arginine-stimulating testing [AST] is not as sensitive for detecting RIH as ITT.[9]) Typically, growth hormone therapy is deemed indicated if peak growth hormone response to ITT is 7 µg/L or less for a child, or 3 µg/L or less for an adult.[9]

A child's rate of growth in stature is also a sensitive measure of growth hormone status, Darzy notes. "In the absence of other etiologies for growth retardation, the presence of significant growth deviation over a 1-year period (ie, growth velocity below the 25th percentile) … is highly suggestive of clinical growth hormone deficiency."[9]

Because growth hormone replacement therapy may not be safe for 1 to 3 years after cancer treatment (the peak-risk period for recurrence, during which time it could facilitate growth of uneradicated tumors), testing usually should not begin within the first year after treatment.[9] Thereafter, if growth rate is appropriate for a patient's pubertal status, Darzy advises that subsequent growth be closely monitored and growth hormone response to ITT be tested annually.[9] A normal ITT result 10 years after radiation exposure "usually eliminates the need for further annual testing," Darzy reports.[9] ■

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