

Effect of Radiotherapy on Endocrine Functions: About A Pediatric Series

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Summary: Patients treated with cranial radiotherapy often develop dysfunction of the hypothalamic–pituitary axis. The endocrine system was the organ system most commonly affected among childhood survivors, Growth hormone is disrupted most often, followed by gonadal, adrenal, and thyroid hormones . The severity and rate of development of hypopituitarism is determined by the dose of radiotherapy delivered to the hypothalamic–pituitary axis. The objective of this study was to report the frequency of anterior pituitary insufficiency post-radiotherapy in children and adolescents

Keywords: Radiotherapy, hypopituitarism, Thyroid insufficiency, Gonadal insufficiency

I. Introduction

Treatment by radiothérapie can put patients at risk of health problems that can develop many years later, most commonly affecting the endocrine system. Patients treated with cranial radiotherapy often develop dysfunction of the hypothalamic–pituitary axis (1). The endocrine system was the organ system most commonly affected among childhood HCT survivors, with upwards of 30% of HCT survivors reporting severe endocrine conditions compared with 5% of non-HCT general cancer survivors (2).

A characteristic pattern of hormone deficiencies develops over several years. Growth hormone is disrupted most often, followed by gonadal, adrenal, and thyroid hormones, leading to abnormal growth and puberty in children, and affecting general wellbeing and fertility in adults. The severity and rate of development of hypopituitarism is determined by the dose of radiotherapy delivered to the hypothalamic–pituitary axis (3).

The objective of our study was to report the frequency of anterior pituitary insufficiency post-radiotherapy in children and adolescents

Population, methodology

20 patients (16 F and 4 M) of median age 16 years (10-18) received radiotherapy for an intracranial tumor (Medulloblastoma n: 4, corticotropic adenomas n: 3, somatotropic adenomas n: 3) nasopharyngeal cancers n: 4 and leukemia n = 6. All patients were referred after this treatment for specialized follow-up in endocrinology. They all benefited from a complete clinical examination, an hypophysigram and annual clinical and hormonal reassessments. When a peripheral glandular origin is suspected, a complementary orientated assessment is performed

II. Result

The hormonal deficiency was found mostly at the annual revaluations (80%). In 20% of the cases, the diagnosis was made in front of signs for which a consultation was carried out

The frequency of somatotropic insufficiency is 20% after 2 years post-radiotherapy 50% After 6 years and 100% after 10 years .. The other axes are reached less frequently and later. The growth hormone deficiency is early for high doses. It is constant and precocious. Gonadotropic insufficiency is the most frequent after the 60% somatotropic insufficiency, Followed by thyrotropic insufficiency 45% and corticotropic insufficiency 30%. No diabetes insipidus was noted. A primary thyroid involvement was observed in 40% of nasopharyngeal cancers.

III. Discussion

The impact of radiotherapy depends upon the involved field, total dose, and schedule. There is a well-established association between the total radiation dose and the development of pituitary hormone deficiencies . The growth hormone (GH) axis is the most sensitive of the hypothalamic functions to radiation and can be affected at doses of 18 Gy irradiation (4). At hypothalamic doses of radiation 1 40 Gy, gonadotropin, corticotropin, and thyrotropin secretion may be compromised. The age of the patient at the time of radiotherapy may affect the degree of hypothalamic-pituitary damage sustained. Some studies suggest that younger age at the time of diagnosis and treatment may lead to more deleterious effects on the hypothalamic-pituitary axis (5) . When a child who has undergone cranial RT presents for care, issues of growth, central hypothyroidism, central adrenal insufficiency, precocious puberty, gonadotropin deficiency, hyperprolactinemia, and obesity must all be considered (6).

GH deficiency is the most common endocrine problem following cranial RT. children treated with cranial RT should undergo semi-annual screening for growth failure by assessing nutritional status, and monitoring of height, weight, and BMI percentiles, as well as sexual maturity rating. Additional considerations include bone age and thyroid studies for poorly growing children. Endocrine consultation should be obtained for children who are below the third percentile for height or weight, have dropped two percentile channels on the growth chart, or are growing slower than 4–5 cm per year (4).

Gonadotropin Deficiency Pubertal stage and maturation should also be assessed in survivors who have undergone cranial radiotherapy. True precocious puberty, early puberty, and normally-timed puberty with rapid progression have been associated with radiation doses of 6–18 Gy; female gender and younger age at treatment are also risk factors (7). Radiation doses ≥ 40 Gy may delay puberty through gonadotropin deficiency (4).

Central hypothyroidism in the setting of cranial radiotherapy is primarily the result of deficiencies of thyrotropin-releasing hormone (hypothalamic) and thyroid-stimulating hormone (pituitary) in children who have received ≥ 40 Gy of radiation. Radiotherapy may also give rise to central adrenal insufficiency. At radiation doses ≥ 40 Gy, the adrenal corticotropin hormone (ACTH) axis may be affected to varying degrees. Because central adrenal insufficiency has been identified in survivors many years after the completion of therapy, an 08:00 a.m. serum cortisol level should be obtained yearly until 15 years off therapy (8). High-dose cranial RT (≥ 40 Gy), mid-brain surgery, or tumor in the hypothalamic area may predispose a child to the development of hyperprolactinemia, which interferes with the pulsatile secretion of gonadotropin-releasing hormone (9). In the female, a history of galactorrhea and menstrual irregularities are of prime importance; in the male, the presence of galactorrhea and decreased libido warrant further evaluation.

Cranial RT may also lead to weight management issues, often exacerbated by concurrent GH deficiency and hypothyroidism. Females, and children ≤ 4 years at the time of treatment, as well as those who have received hypothalamic radiation doses ≥ 18 Gy are at particular risk (4). Additional considerations include the assessment of other co-morbid conditions including dyslipidemia, hypertension, glucose intolerance, diabetes mellitus, hyperinsulinism, and insulin resistance. Apart from cranial irradiation, target-organ irradiation involving the neck, abdomen, pelvis, and testes has the most pronounced endocrine late effects. With radiation doses in excess of 10 Gy in the region of the thyroid, hypothyroidism or, rarely, hyperthyroidism may occur. Irradiation to the thyroid, especially at doses ≥ 25 Gy, may also predispose to the development of thyroid nodules; thus annual thyroid palpation is important during physical examination. Thyroid cancer may also develop after radiation to the neck. Recent evidence shows increasing risk with doses up to 30 Gy and then decreasing risk for thyroid cancer with higher doses of radiation (9)(10)(11)(12).

Total body irradiation (TBI), abdominal, pelvic and lumbosacral spine radiation, especially in the postpubertal female, can compromise ovarian function. Mounting evidence suggests increased risk for premature menopause that must be factored into the long-term counseling of young adult survivors. Women at highest risk include pubertal females treated with ≥ 10 Gy, and those who have received high doses of alkylating agents (see Chemotherapy section). The testes are particularly sensitive to radiation, with germ cells suffering damage at much lower levels of radiation than Leydig cells [30–32]. The effect of testicular irradiation is highly dose-dependent. At doses of 1–3 Gy, azoospermia may be reversible; at 3–6 Gy, this reversibility is much less likely. Over 6 Gy, the patient is likely to suffer from permanent azoospermia. Doses ≥ 20 Gy may cause Leydig cell damage and affect production of testosterone (13).

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