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REVIEW ARTICLE

Endocrine consequences of childhood malignancies

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Summary

Advances in cancer therapy over the last years have resulted in improved survival rates for pediatric cancer patients. However, new treatments are associated with short and long-term morbidity. The endocrine system is particularly sensitive to cancer therapies. Long-term survivors of childhood cancer are at risk for hypothalamic pituitary dysfunction, gonadal failure or disorders relating to pubertal progress, thyroid disease, obesity, disorders of lipid metabolism and disorders of bone and mineral metabolism. Long-term follow-up is indicated, as these disorders may not become apparent until adulthood.

Key words: childhood cancer, gonadal failure, growth hormone deficiency, long-term survivors, obesity

Introduction

About 200,000 children have been estimated to develop cancer each year, based on data from a world population of 1,65 billion children [1]. Advances in oncological therapy in combination with improved supportive care have resulted in increased survival rates for children with cancer. Thus, the overall survival rate for pediatric cancer is calculated over 70% [1,2] and it has been estimated that 1 in 1,000 adults between 20 and 30 years of age are survivors of childhood cancer [1,3]. However, these significant survival benefits are associated with short and long-term morbidity resulting from treatment regimens' toxicities. Endocrine deficiencies are particularly frequent in survivors of childhood cancer, as the endocrine system is vulnerable to the effects of chemotherapy and radiotherapy [4,5]. The Childhood Cancer Survivor Study (CCSS), which is a retrospective cohort study that included 14,000 childhood cancer survivors and 4,000 sibling controls, confirmed a high prevalence of chronic complications with 62% of children reporting one, 24% three and 28% a severe or life-threatening complication [6]. The cumulative incidence of complications reaches 70% by 30 years after cancer [6].

Growth

Survivors of pediatric cancer who received cranial irradiation achieve final height significantly below predicted from parental heights [7,8]. Both nonendocrine and endocrine factors are responsible.

Nonendocrine factors include poor nutritional intake, spinal irradiation and effect of intensive chemotherapy. The effect of spinal irradiation on final height depends on the dose and volume of radiation as well as the age of the patient at irradiation [8]. The younger the age of the child at the time of radiotherapy, the more pronounced the effect [7]. Adjuvant chemotherapy potentiates the radiation-induced growth failure [9] by amplifying the damage of the hypothalamic-pituitary axis caused by irradiation [10], directly affecting the production of insulin-like growth factor-1 (IGF-1) by the liver [11], or impairing the action of IGF-1 on the growth plate [9].

Endocrine factors include growth hormone deficiency, hypothyroidism and precocious or early puberty. These disorders are most related to radiation-induced toxicity and are also dependent on the total dose, fractionation schedule, age, and duration of treatment [8,12].

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Growth hormone deficiency (GHD)

GHD can be observed in children with tumors located in the region of the hypothalamus and pituitary as a result of the tumor itself or the surgical procedures for the resection of the tumor [13,14]. More commonly, however, GHD results from the radiotherapy of the primary malignancy. The severity of the deficiency depends on the radiation dose, the fractionation schedule and the interval after radiation. Lower doses of radiation, as used in the treatment of acute lymphoblastic leukemia (ALL) or brain tumors (18-50 Gy) usually result in isolated GHD, mainly because of damage to the more radiosensitive hypothalamus [13], whereas higher doses (greater than 60 Gy) may additionally produce anterior pituitary damage which contributes to early and multiple pituitary hormone deficiencies [15]. Interestingly, however, radiation to the hypothalamic-pituitary axis does not produce diabetes insipidus. The same total dose given in fewer fractions over a shorter period of time results in a higher incidence of pituitary hormone deficiency than if the schedule is spread over a longer time interval with a greater number of fractions [16]. Recently, the degree of anterior pituitary hormone deficiency has been associated with the biological effective dose (BED) of radiation which is calculated according to a formula incorporating total dose, fraction size and tissue response to radiation and is used to predict the effect on the hypothalamic-pituitary function [17]. Also, an increase in the frequency and severity of hormonal deficiency is observed with a longer time interval after radiotherapy, due to the delayed effects of radiotherapy on the axis and/or the development of secondary pituitary atrophy following initial hypothalamic damage [17]. Some chemotherapeutic agents have also been shown to potentiate the negative effect of radiation on the pituitary function [18], but there is no proof that chemotherapy alone leads to neuroendocrine dysfunction.

Thus, children with central nervous system (CNS) tumors and tumors of the orbit and face (gliomas, medulloblastomas, germinomas, ependymomas, astrocytomas, orbital rhabdomyosarcomas, neuroblastomas) usually experience growth failure and GHD, especially when they have additional spinal irradiation [19]. The exact incidence of radiation induced GHD and/or neurosecretory dysfunction is not well-defined, since reported frequencies depend on the type of investigation used to assess it (provocative tests, spontaneous secretion, 24 h secretion) and the time interval after radiotherapy. Children with hematological malignancies i.e. ALL generally receive lower doses of CNS radiation or no cranial irradiation and the prevalence of GHD is much lower [20]. Concerning children with hematological malignancies who are treated with bone marrow transplantation and total body irradiation (cranial irradiation excluded), they usually present a blunted pubertal growth spurt at appropriate age [21].

Gonadal function

Gonadotropin deficiency

The effect of radiation on the hypothalamic-pituitary-gonadal axis is dose-dependent. Doses greater than 50 Gy produce gonadotropin deficiency, whereas lower doses may result in early puberty.

Thus, when doses greater than 50 Gy are used in the treatment of brain tumors, there is increased incidence of gonadotropin deficiency. The prevalence of gonadotropin deficiency increases with post-irradiation interval with a cumulative incidence of 20-50% reported in long-term followed patients [22], and constitutes the second most common anterior pituitary hormone deficiency.

Low-dose radiation, as employed in CNS prophylaxis for ALL, is associated with early puberty which predominantly affects girls [23]. Higher doses used in the treatment of brain tumors (25-50 Gy) may lead to early puberty in both sexes [24] with a linear correlation between age at the onset of puberty and age at irradiation.

Primary gonadal failure

The effect of chemotherapy and radiotherapy on gonadal function is sex-specific. In males, Sertoli cells are more sensitive than Leydig cells to both chemotherapy and radiotherapy [25]. Consequently, impaired spermatogenesis and infertility are usually observed, while androgen treatment is rarely required, except after direct testicular irradiation at doses greater than 20 Gy [26]. Younger boys are at less risk than older boys and male adults [27].

The ovaries are less sensitive than the testes to gonadotoxic agents and chemotherapy. Gonadotoxicity is dose-dependent and can occur with the following chemotherapy agents: alkylating agents, procarbazine, cisplatin and vinblastine. Alkylator chemotherapy may result in irregular menses or early menopause [28]. Chemotherapy is more destructive to ovaries after pubertal onset, compared with therapy at younger ages. Radiation-induced ovarian failure is dose-dependent and younger girls are at less risk than older females. In females sex steroid production and germ cells are lost in

parallel. Loss of sex steroid production may manifest as failure to enter or progress through puberty, or premature menopause and/or problems of fertility in later adult life. At radiation doses greater than 50 Gy, complete ovarian failure is frequent [27]. Scattered radiation from spinal radiotherapy, as used for treatment of ALL and brain tumors, can also result in gonadal damage [29,30].

The CCSS study showed development of acute ovarian failure within 5 years of tumor diagnosis in 6.3% of women aged more than 18 years [31]. Risk factors for acute ovarian failure were older age at tumor diagnosis, Hodgkin's lymphoma, ovarian irradiation >10 Gy or alkylating agents at age 13-20 years. In a separate analysis, excluding cases with acute ovarian failure, 4.5% of the survivors developed premature menopause [32], out of whom 50% had non-surgical premature menopause (relative risk 13.2 compared with siblings). Alkylating agents plus abdominopelvic irradiation resulted in cumulative incidence of premature menopause of approximately 30%.

Thyroid function

Thyroid stimulating hormone (TSH) deficiency

Among pituitary hormones, TSH is the last hormone to be affected and the hypothalamic-pituitary-thyroid axis the least vulnerable to radiation damage. The prevalence of radiation-induced TSH deficiency has been shown to be related to the dose and the time interval following irradiation [24,33].

The prevalence of central hypothyroidism following irradiation varies greatly in different studies, depending on the method of diagnosis. In most studies, where diagnosis is based on TSH and T4 measurements, the prevalence of central hypothyroidism is reported to be only 6% [33,34]. In another study, however, where diagnosis was based on thyrotropin-releasing hormone (TRH) test, central hypothyroidism was diagnosed in 36% of cancer survivors after a mean of 6 years follow-up [35].

Primary thyroid damage

The thyroid gland in children is one of the most sensitive organs to damage from radiation. All kinds of thyroid disorders have been described: hypothyroidism, hyperthyroidism, thyroid nodules [36].

Compensated or frank hypothyroidism has been reported in 20-60% of brain tumor survivors depending on treatment methods and length of follow-up [33, 37]. The thyroid damage can be the result of either the cranial irradiation alone or the scattered radiation from craniospinal irradiation [33]. Prior exposure to iodine-containing contrast material and younger age at treatment increases the risk of development of hypothyroidism [2]. The use of adjuvant chemotherapy also increases the incidence of hypothyroidism in most [34, 36] but not in all studies [33,38,39].

Increased risk for thyroid cancer has also been reported following radiotherapy for head, neck and upper thorax. In the CSSS study, the risk increased with increasing radiation doses up to 20-29 Gy [40], but decreased at higher doses [41], consistent with a cell-killing effect. Risk is higher for younger children, females and for survivors of Hodgkin's lymphoma and neuroblastoma [41]. Thyroid nodules occur frequently in irradiated people and the percentage of nodules with malignancy in cancer survivors varies from 14 to 40% [42]. Radiation-induced tumors begin to appear 5-10 years after irradiation and increased risk persists for decades [43].

Adrenal function

The hypothalamic-pituitary-adrenal (HPA) axis may be affected relatively late by irradiation. Most studies based on less than 12 years follow-up after cranial irradiation for childhood brain tumors demonstrated only subtle abnormalities in the HPA axis [18,24,44], whereas a recent study reported 19% abnormalities after 15 years of follow-up [45]. The risk of damage to the HPA axis is also dose-dependent, since low doses of irradiation (18-24 Gy), which are used in the treatment of ALL, seem to have no effect on it [45]. Concerning the method used for detection of ACTH deficiency, it must be noticed that insulin tolerance test (ITT) is the gold standard and glucagon stimulation test (GST) is comparable, whereas the short synacthen test is less reliable [45]. Monitoring of brain tumor survivors for ACTH deficiency must continue beyond 10 years following irradiation and preferably with ITT or GST. Moreover, potential temporary suppression of the HPA axis with transient adrenal insufficiency can be produced by high-dose glucocorticoid therapy used in induction protocols [46].

Obesity and cardiovascular risk

Obesity is another late effect in cancer survivors. It has been suggested that obesity is due to damage to the ventromedial hypothalamus which regulates the

energy balance [47]. Craniopharyngioma patients may suffer hypothalamic damage from the tumor itself, surgery and irradiation [48]. Sleepiness and narcolepsy with decreased physical activity may also be present in these patients [49]. Obesity and related cardiovascular risk factors have been demonstrated in survivors of other malignancies. Hypothalamic damage from radiation, particularly in high doses (≥50 Gy), in brain tumor survivors was associated with body mass index (BMI) increases 10 years after therapy [50]. Similar observations were made in young adult survivors of ALL [51]. In another study however, no significant differences in BMI and fat mass were observed between long-term survivors of ALL and controls [52].

Glucocorticoids could also promote obesity, but studies in ALL survivors have been inconclusive in demonstrating an association between weight gain and steroids used [53]. GHD when caused by radiation can also contribute to the development of obesity and GH therapy can improve weight [54]. Increases in serum leptin and leptin per unit of fat mass were associated with increasing degrees of GHD in a cohort of long-term survivors of ALL [52]. Although, this hyperleptinemia may be associated with GHD, it may also be the direct effect of irradiation on the hypothalamus, resulting to leptin insensitivity.

Another possible mechanism leading to obesity are the neurological complications caused by intracranial tumors and their treatment, which affect physical activity and predispose to obesity [55]. In a CCSS study, no significant differences in BMI between brain tumor survivors and siblings controls [8] have been demonstrated, but survivors from ALL were twice as likely to be obese as siblings [56]. Also total body irradiation (TBI) in survivors of hematopoietic cell transplant has been shown to contribute to the development to insulin resistance/diabetes but not to an increased obesity risk [56].

Finally, a significant number of childhood cancer survivors, besides obesity, can demonstrate glucose intolerance, hyperinsulinemia and abnormal lipid profile [55,57], fulfilling the criteria of metabolic syndrome which is known to be associated with increased cardiovascular risk.

Metabolic bone disorders

Osteopenia, osteoporosis, and even fractures have been reported in long-term survivors after childhood cancer therapy [58]. Reduction in BMI is a consistent finding in survivors of childhood cancers. In the majority of the studies BMI has been evaluated by Dual-Energy-X-ray Absorptiometry (DEXA) and results are consistent that BMI was reduced [59-62]. The exact contribution of GHD in these studies is difficult to differentiate from the effect of the disease itself and the effect that therapy may have induced on bone accretion. Children with cancer may present at diagnosis with decreased bone formation and normal bone resorption. After chemotherapy, bone formation may be normalized, but bone resorption has been reported to be increased [59-62]. Exposure to glucocorticoids, methotrexate or both may also have contributed to osteopenia observed in these patients.

Conclusion

Continued surveillance is necessary in children, adolescents and young adults, who have received chemotherapy or irradiation as part of treatment modalities for childhood malignancies, to achieve early diagnosis and treatment of endocrine and other sequelae. Monitoring of statural growth must be made on a 6-month basis before fusion of growth plates and in case of decline in growth velocity, GH secretion must be evaluated. Pubertal status and thyroid function must be evaluated at 6-month intervals. HPA axis monitoring must begin with an early morning cortisol level. Body composition, bone density and lipid levels must also be monitored periodically.

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