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ERİŞKİN YAŞA GELEN ÇOCUKLUK ÇAĞI VE ADOLESAN KANSER HASTALARINDA DİĞER NONREPRODÜKTİF ENDOKRİN ANORMALLİKLER

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ÖZET

Erişkin yaşa gelen çocukluk çağı kanser hastalarında tedaviye bağlı olarak pekçok sitemik ve endokrin bozukluk izlenmektedir. Malesef kız cinsiyet bu olumsuzluklardan daha fazla pay almaktadır. Özellikle kraniospinal radyasyon sonrası, kognitif bozukluklar, obesite, kardiovasküler hastalık, pubertenin zamanlamasına aksaklık, tiroid fonskiyon bozuklukları, iskelet büyümesinde gerilik bunlardan bir kaçıdır. Bu bülümde bu hastalarda uzun dönemde görülen üreme dışı endokrin anormallikler işlenecektir.

ABSTRACT

There are numerous treatment-related risks for long-term adverse outcomes among survivors of childhood cancer after exposure to chemotherapeutic drugs and radiotherapy. Sadly, It appears that female sex is more commonly associated with treatment related risks such as cognitive dysfunction after cranial irradiation, poor cardiovascular outcomes, obesity, radiation-associated differences in pubertal timing, development of primary hypothyroidism, impaired skeletal growth breast cancer as a second malignant neoplasm, and osteonecrosis.

OTHER LONG-TERM ENDOCRINE ABNORMALITIES IN THE CHILDHOOD CANCER SURVIVORS

There are a number of long-term morbidities that follows the treatment of childhood cancer. the Childhood Cancer Survivor Study provided important data on long term outcomes of survivors of pediatric cancer. It is a retrospective cohort study that tracks the health status of adults who received a diagnosis of childhood cancer between 1970 and 1986. The study has documented an exceptionally high incidence of chronic conditions among 10,397 survivors (mean ages of 26.6 years (range, 18.0 to 48.0)) compared to siblings (mean age 29.2 years (range, 18.0 to 56.0)). 62.3%had at least one chronic condition; 27.5%had a severe or life-threatening. The cumulative incidence of a chronic health condition reached 73.4%(95%CI, 69.0 to 77.9) 30 years after the cancer diagnosis, with a cumulative incidence of 42.4%(95%CI, 33.7 to 51.2) (1). Endocrine abnormalities are the most frequently reported complications in the survivors of childhood cancers (2). Table summarizes common endocrine dysfunctions observed in the survivors. These complications frequently occur as late effects of cancer treatments affecting between 20 and 50%of individuals (3). Patients exposed to radiotherapy and high doses of alkylating agents prior to hematopoietic stem cell transplantation, survivors of central nervous system (CNS) tumors, and Hodgkin's lymphoma are at particularly high risk of developing endocrine complications. Being mainly endocrine in origin these complications arise due to therapy-related damage to key endocrine organs such as the hypothalamic–

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Tablo I—Other Endocrine Dysfunctions Diagnosed in the Survivors Of Pediatric Cancer Patients

System	Function	Complication	Cause	Dose
Hypothalamic-pituitary axis	Puberty	Precocious puberty	Cranial irradiation	• Cranial irradiation at both lower doses (18–35 Gy) and higher doses (>35 Gy) may lead to precocious puberty by disrupting inhibitory cortical influences (2) .
Hypothalamic-pituitary axis	Puberty	Hypogonadotropic hypogonadism	Cranial irradiation	Radiation > 50 Gy may cause hypogonadotropic hypogonadism along with deficiencies of other pituitary hormones (2).
Hypothalamic-pituitary axis	Linear growth	Growth hormone deficiency	Cranial irradiation Total body irradiation Direct insult to the pituitary by tumoral extension or ablative surgery	The incidence of GH deficiency is 93% at 4 years after 44 Gy irradiation to hypothalamic-pituitary region (18). Doses >30 Gy: effect by 5 years following exposure. Cumulative incidence 90% over 4 years. Doses 18–24 Gy: effect may not become evident for>10 years following the exposure (2).
Hypothalamic-pituitary axis	Metabolism	TSH deficiency	Cranial irradiation (Radiotherapy to hypothalamic–pituitary region)	Doses >30 Gy Cumulative incidence 23% over 4 years for patients treated with doses >42 Gy (2)
Hypothalamic-pituitary axis	Metabolism	ACTH deficiency	Cranial irradiation	Doses >30 Gy: Cumulative incidence 38% over 4 years (2).
Skeletal	Growth	Skeletal dysplasia	Irradiation of the spine and epiphyses	
Thyroid	Metabolism	TSH deficiency Primary hypothyroidism	Cranial radiotherapy Total body irradiation Radioactive iodine Labeled antibodies	
Adrenals	Metabolism	ACTH deficiency	Direct insult (surgery, tumoral expansion) Cranial radiotherapy Glucocorticoids (transient)	

pituitary axis, the thyroid gland, and the gonads; they can also affect bone mass and alter body composition and glucose homeostasis (2).

Puberty

Of particular interest there are two important nongonadal reproductive adverse outcomes in chilhood cancer survivors related to the impact of cancer therapy on hypothalamic-pituitary axis; precocious puberty and hypogonadotropic hypogonadism.

Precocious puberty is defined as the occurrence of puberty before the age of 8 years in girls. Cranial irradiation at both lower doses (18–35 Gy) and higher doses (>35 Gy) may lead to precocious puberty by disrupting inhibitory cortical influences (2). However, when the dose of radiation exceeds 50 Gy hypogonadotropic hypogonadism may ensue along with a maltitude of deficiencies of other pituitary hormones (4). In addition to hypothalamic radiation female sex, young age and increased BMI are the risk factors for central precocious puberty (5). Survivors of CNS tumors are more likely to have onset of menarche before age 10 years compared with their siblings (odds ratio (OR), 14.1; 95%confidence interval (95%CI), 7.0-30.9) (4). An age 4 year at the time of diagnosis increases the risk of early menarche along with a history of radiation to the hypothalamus–pituitary area. Sex steroid driven growth spurt is the earliest sign of puberty and may cause rapid bone age progression and further reduce the growth potential of children, most of whom carry additional risk factors for growth failure such as growth hormone deficiency and radiation-induced skeletal dysplasia. Breast development (telarche) before age 8 and the onset of other secondary sexual characteristics (e.g.pubic hair) prior to the age of 9 years are other signs of puberty that should alert clinicians for the suspicion of precocious puberty. It is important to note that children with precocious puberty who also are likely to have growth hormone deficiency may exhibit falsely reassuring 'normal' growth velocity. In these cases skeletal maturation can be assessed using the standard bone age (X-ray examination of the left wrist and hand). Advancement of the bone age more than 2 S.D. for chronological age is a consistent finding in children with precocious puberty (2). Ultrasound examination of the reproductive system is an important of workup in girls with precocious puberty to document uterine growth on the pelvic ultrasound, which is a sign of estrogenic stimulation, and is generally an earlier finding than bilaterally enlarged ovaries (2) (6).

Delayed menarche has been reported in childhood cancer survivors due to deficits of LH and FSH secretion following irradiation of the hypothalamic-pituitary region. Radiation to sellar region > 30-40 Gy may cause hypogonadotropic hypogonadism albeit less often than growth hormone deficiency. Indeed, In a recent report from the CCSS, female survivors with a history of exposure to doses of radiation >30 Gy to the hypothalamic–pituitary area were less likely to experience a pregnancy (7). Late menarche (defined by the onset of menses after age 16) was reported in 10.6%of the survivors (4). Subtle defects in gonadotropin secretion has been described in radiation doses in the 18-24 Gy range (8).

Growth

Impairment in linear growth and short stature in adulthood are commonly observed in childhood cancer survivors. Growth hormone deficiency, central precocious puberty and primary hypothyroidism are endocrine factors that can contribute to growth retardation. Cumulative incidence of growth hormone deficiency is about 90%in four years post-exposure to radiation to hypothalamic-pituitary area at doses > 30 Gy (2). The deficiency may manifest itself later on (up to ten years postexposure) if radiation is used at lower doses. In addition, direct damage to growing epiphyseal plates, mainly vertebrae after high dose radiotherapy or total body irradiation will cause skeletal dysplasia and impaired linear growth since epiphyseal growth plate are exquisitely sensitive to radiation (2, 9). Interestingly such an adverse effect on the growing plate has not been observed after high dose chemotherapy (10).

Other Endocrine Abnormalities

Obesity and disorders of glucose metabolism and thyroid gland and adrenal cortical trophic hormone (ACTH) deficiency are other endocrine disturbances described in the survivors of childhood cancers. Increased body weight and obesity are commonly observed in the survivors of ALL and brain tumors (11-12). Cranial irradiation, dexametahasone therapy,

female gender and young age (<4 years of age), being homozygous for a polymorphism in the leptin gene are risk factors for obesity (11, 13). Growth hormone deficiency, sellar tumors (by disrupting hypothalamic-pituitary functions), hyperphagia and hyperinsulinemia are other proposed factors contributing to obesity (2). Overt diabetes may also develop in the survivors primarily due to insulin resistance. The main risk factors include total body irradiation, abdominal irradiation and alkylating agents (14).

Abnormalities in thyroid function are among the most commmon endocrine dysfunction diagnosed in the survivors of childhood cancers. Of thyroid dysfunctions primary hypothyroidism is the most common one and frequently develops following exposure of the gland to radiation. This exposure can occur in individuals treated with the following types of radiation: neck/mantle irradiation for Hodgkin's lymphoma; craniospinal irradiation for brain tumors; or TBI for cytoreduction before HSCT (2). Chemotherapy alone does not seem to be associated with an increased incidence of primary hypothyroidism (15). Total dose of the radiation, duration of the follow-up, female gender, white race, and age >15 years at the time of diagnosis are risk factors for developing primary hypothyroidism (2, 16). In a large study from the CCSS on young adult survivors of Hodgkin's lymphoma, a cumulative incidence of hypothyroidism of 28%was observed; for those treated with doses >45 Gy, there was a 50%incidence of hypothyroidism 20 years after diagnosis (17). Central hypothyroidism after TSH deficiency is another form of thyroid dysfunction reported in the survivors of childhood cancers. In a study on children receiving treatment for CNS embryonal tumors resulting in high doses of radiation to hypothalamus–pituitary area, the cumulative incidence of TSH deficiency was 23%at 4 years with a significant risk for patients with doses to the hypothalamic–pituitary area above 42 Gy (18). Chemotherapy alone does not seem to be associated with central hypothyroidism.

ACTH deficiency may occur due to the prolonged use of glucocorticoids. But this form is relatively uncommon in childhood cancer survivors. Rather, tumor extension or radiation to hypothalamic-pituitary region (>30 Gy) are more common causes. 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).

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