

Endocrine Effects of Childhood Cancer and Transitioning to Adult Endocrine Care

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Objectives

- Recognize the challenges of transition of childhood cancer survivors from pediatric to adult care
- Recognize the risk of growth hormone deficiency and the outcomes of its therapy in childhood cancer survivors
- Recognize the risk of other anterior pituitary hormone deficiencies in childhood cancer survivors

Background

Childhood cancer survivors (CCS) are surviving into adulthood at an increasing rate, so understanding the transition process and the needs of these individuals is important. Transition is defined by The Society for Adolescent Health and Medicine as the “purposeful, planned movement from adolescents and young adults (AYA) with chronic and physical medical conditions from child-centered care to the adult-oriented health care system” (1).

Since 1975, there has been an increase by 0.6% per year in the incidence rate of cancer in children ages 0-14 years (2), and it was estimated that 15,270 children and adolescents age 0-19 years old would be diagnosed with cancer in the United States in 2017. Survival has also risen due to improvements in therapy. The overall 5-year survival rate was 50% in 1975 and 83% in 2007-2013 (3), and late mortality has declined as treatment exposures have decreased (4). Additionally, the number of children in the United States is increasing (73.6 million in 2016 and estimated to be 79.9 million in 2050) (5). As of 01/01/2014, there were approximately 419,000 individuals in the United States who were survivors of childhood cancer (3).

Chronic health conditions are common in adult CCS and increase over time, with endocrine disorders being the most common (6,7). Other frequent conditions include secondary malignancies, cardiovascular disease, renal dysfunction, and severe musculoskeletal problems. In a study of 10,397 CCS at median age 26.6 years (range 18.0 – 48.0), 62.3% had at least one chronic disorder (8). In a study of 310 Italian adult CCS with history of intracranial and non-intracranial malignancies, 57% had developed an endocrine disorder at a median age of 25.31 years at a median of 16.38 years after cancer diagnosis (6). Radiation therapy and alkylating agent chemotherapy are the treatment risk factors most highly associated with the development of endocrine late effects (9). The prevalence and incidence rates of endocrine late effects vary due to the population studied (different diagnoses, different treatment exposures, small sample sizes), length of follow-up, screening methods, lack of standardization of laboratory assays, diagnostic thresholds, and other factors such as genetics.

Transition

The transition process from pediatric to adult endocrine care of CCS has not been studied, although Schwartz *et al* have developed and validated a transition tool (10). In general, the transition process requires the readiness of the provider, family, and patient (11) and should start in early adolescence and occur over multiple visits over multiple years:

- Discussion of office transitions policy with youth and parents at 12-13 years of age
- Initiation of a jointly developed transition plan with youth and parents at 14-15 years of age
- Reviewing and updating transitions plan and preparing for adult care at 16-17 years of age
- Implementing adult model at ≥ 18 years of age (12), with recommendation that patients transition from pediatric to adult care between 18 and 21 years of age

(11).

CCS may need to transition their care at an older age because of multiple chronic health conditions, cognitive late effects, problems with psychosocial functioning, delayed physical development, and dependence on their parent(s)/caregiver(s) (10,13). Therefore, the transition process requires individualization. CCS who have recently finished cancer-directed therapy or who are at a higher risk of late effects are more likely to indicate a preference to either never transition to adult care or to transition at an older age (14). Regardless, transition of endocrine care should occur (15).

While adolescent CCS would like to gradually assume responsibility for their own health care and see providers by themselves, they also want ongoing support from their parent(s)/caregiver(s) for scheduling appointments, medical decision-making, and dealing with new clinical symptoms (16). Because of ongoing involvement by their parent(s)/caregiver(s), some CCS may not know about their past and current medical history, its significance, or their need for long-term assessment (17). The adult endocrine provider may need to interact with the parent(s)/caregiver(s) more than they are used to doing, especially when the parent(s)/caregiver(s) have to help the patient in activities of daily living due to their physical and/or cognitive limitations (13).

Assessment of transition readiness of the AYA includes reviewing and confirming their understanding of their illness, medications, when to seek routine and emergency care, etc. Patients should also receive a summary of their diagnoses and treatment course (“transfer letter”). While not specific to CCS, the website <http://www.endocrinetransitions.org/> has a checklist for skills assessment for individuals with hypopituitarism.

Anterior Pituitary Hormone Deficiencies in the CCS

Anterior pituitary hormone deficiencies occur as a result of hypothalamic-pituitary (HP) tumors or from radiation therapy to the HP axis, directly related to radiation dose and inversely related to the number of radiation fraction. In the St. Jude Lifetime Cohort Study (SJLIFE) of 748 adult CCS at a mean age of 34.2 years who had been treated with cranial radiation and observed for a mean of 27.3 years, 46.5% had growth hormone deficiency (GHD), 10.8% had gonadotropin deficiency, 7.5% had thyrotropin deficiency (TSHD), and 4% had adrenocorticotropin deficiency (ACTHD) (18); likely underestimates, as diagnoses were based on criteria that increased sensitivity but lowered specificity. The risk for endocrine late effects does not appear to level off, so life-long evaluation will be necessary (19).

Adult GHD

GHD is the most prevalent anterior pituitary hormone deficiency in CCS. The main risk factors for GHD are HP injury due to direct tumor effect or surgery, as well as radiation therapy to the HP axis. The risk of GHD is directly related to radiation dose and inversely related to the number of radiation fractions and can occur after ≥ 18 Gy (9). In the Childhood Cancer Survivor Study (CCSS) cohort, the cumulative incidence of GHD after ≥ 18 Gy was 17.3% within 15 years, although cases may have been missed because of lack of systematic evaluation (19). GHD can also occur after a single TBI dose of 10 Gy or fractionated doses of 12 Gy (9), however, there can be recovery over time (20).

In comparison to those with treated GHD, untreated adult CCS are more likely to have increased waist-to-height-ratio, decreased lean muscle mass and muscle weakness, poor exercise tolerance, and low energy expenditure (18). Some studies suggest GH therapy improves these metabolic parameters and quality of life, although outcome data are limited. In evaluation for adult GHD in CCS, growth hormone releasing hormone alone, or in combination with arginine, should not be used; the damage is primarily hypothalamic, and testing may give a false negative result (9). Similar to the non-CCS, insulin-induced hypoglycemia is considered the most reliable test (21).

Concern has been raised about GH therapy inducing secondary neoplasms (SN) or tumor recurrence, as GH and IGF-I have mitogenic properties, stimulate cellular proliferation, and inhibit apoptosis in *in vitro* assays (22). Radiation therapy is the most common cause of SN, and after cranial radiation, there is an increased risk of the development of meningiomas and gliomas. Initial data from the CCSS suggested that the risk of SN in children treated with GH relative to those not treated was 3.21 (95% 1.88-5.46), with meningioma most common (23); after longer follow-up, the risk decreased to 2.15 (95% 1.3-3.5) (24). Even more recent data from the same cohort showed no significant association between GH therapy and the development of a central nervous system SN (25). Other studies have had similar findings (26). These same studies have also not shown a significant increased risk of tumor recurrence after GH treatment. Data on GH replacement in adult CCS is more limited. Mackenzie *et al* found no difference in

the incidence rate of SN in GH-treated vs. non-GH treated patients at a median follow up of 14.5 years after cranial radiation (110 patients with median of 8 years of GH treatment, range 4-10 [69 adult onset tumors] and 110 controls [68 adult onset tumors]) (26). A post-market surveillance study after only 2.9 years follow-up of GH-treated patients (1.5, 5.1) and 2.6 years of controls (1.8, 3.7) found a similar SN proportion in GH-treated of 6.0% (95% CI, 3.4 - 9.6%) vs. non-GH treated of 7.1% (95% CI, 0.9 - 23.5%) (22).

Other Anterior Pituitary Hormone Deficiencies

The main risk factors for other anterior pituitary hormone deficiencies are HP injury due to direct tumor effect or surgery, or radiation doses ≥ 30 G, although patients treated with lower doses of radiation may develop these deficiencies over time. After HP radiotherapy, the prevalence of gonadotropin deficiency has been reported as 11%, of TSHD at 7.5-9.2%, and of ACTHD at 4-5% (9). Anterior pituitary hormone deficiencies are evaluated in the same way as for non-CCS. Other endocrine and medical conditions may confound the interpretation of screening lab tests. Obesity may decrease sex hormone binding globulin leading to low total testosterone levels (27). Non-enzyme inducing anticonvulsant medications (e.g., lamotrigine, valproate and levetiracetam) can cause changes in plasma sex hormone concentrations (28). Some anticonvulsant medications (e.g., phenytoin, carbamazepine, and oxcarbamazepine) can increase nondeiodinative metabolism of thyroid hormone metabolism and its displacement from binding proteins leading to artifactually low free T4 levels in the commonly used free T4 assays that use competitive binding methods (29). Oral contraceptive pills lead to elevation in cortisol binding globulin resulting in increased cortisol levels (30).

Conclusions

Endocrine disorders are common late effects of treatment of childhood cancer. Anterior pituitary hormone deficiencies can develop secondary to tumors in the HP location and/or their resection or to cranial RT. Therapy goals and monitoring of treatment of anterior pituitary hormone deficiencies may change from childhood to adulthood making transition from a pediatric to an adult provider appropriate. However, this transfer of care may be more challenging than in other populations due to the presence of other chronic morbidities and developmental and cognitive delays.

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