DIAGNOSIS OF ENDOCRINE DISEASE

Endocrine late-effects of childhood cancer and its treatments

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Abstract

Endocrine complications are frequently observed in childhood cancer survivors (CCS). One of two CCS will experience at least one endocrine complication during the course of his/her lifespan, most commonly as a late-effect of cancer treatments, especially radiotherapy and alkylating agent chemotherapy. Endocrine late-effects include impairments of the hypothalamus/pituitary, thyroid and gonads, as well as decreased bone mineral density and metabolic derangements leading to obesity and/or diabetes mellitus. A systematic approach where CCS are screened for endocrine late-effects based on their cancer history and treatment exposures may improve health outcomes by allowing the early diagnosis and treatment of these complications.

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Introduction

Childhood cancer cure rates have substantially improved over the past five decades, resulting in a growing number of long-term survivors. In the USA, it is estimated that one out of 530 adults in their second or third decade of life is a childhood cancer survivor (CCS) (1). Progress in this field is owed to treatments incorporating chemotherapy and/or radiotherapy in conjunction with supportive care to address acute complications. Surviving patients

may go on to experience late-onset chronic health conditions months to decades after the primary cancer; such conditions are described as late-effects (2). Endocrine complications are among the most common late-effects in CCS and they frequently occur because of exposures to radiotherapy and/or alkylating agent chemotherapy. It is estimated that 50% of CCS will experience at least one endocrine or reproductive complication during the

Invited Author's Profile

Dr Wassim Chemaitilly currently serves as the Director of the Endocrinology Division at St Jude Children's Research Hospital in Memphis, Tennessee, USA and has a joint faculty appointment with the institution's Department of Epidemiology and Cancer Control where he conducts most of his clinical research. He is a pediatric endocrinologist with established interest in the long-term adverse effects of cancer and brain tumor treatments on the endocrine system. Dr Chemaitilly obtained his Medical Doctorate degree and Pediatric Medicine diploma at the Université René Descartes – Necker Enfants Malades in Paris, France before completing a Pediatric Endocrinology fellowship at New York Presbyterian Hospital, Weill Cornell Medical College in New York City in 2006.

course of his/her lifetime (3). The present manuscript offers a summary of the main endocrine late-effects in CCS including hypothalamic/pituitary (HP) axis dysfunction and complications affecting the thyroid and gonads, as well as decreased bone mineral density (BMD) and metabolic derangements leading to obesity and/or diabetes mellitus.

HP axis dysfunction

HP axis dysfunction includes the following disorders: growth hormone (GH) deficiency (GHD), central precocious puberty (CPP), luteinizing hormone (LH)/follicle-stimulating hormone (FSH) deficiency (LH/FSHD), thyroid-stimulating hormone (TSH) deficiency (TSHD), adrenocorticotrophic hormone (ACTH) deficiency (ACTHD), hyperprolactinemia and central diabetes insipidus. HP axis dysfunction is frequently observed in survivors of central nervous system (CNS) tumors and those whose HP region was exposed to radiation (4). Data supporting associations between conventional chemotherapy and irreversible HP axis dysfunction are limited (5, 6, 7). Novel targeted chemotherapy agents such as tyrosine kinase inhibitors (TKI) (8, 9) and immune system modulators (10) seem to be associated with HP disorders.

The presentation of HP axis dysfunction varies according to tumor location and treatment modalities. Patients experiencing direct HP injury related to local tumor growth or surgical resection generally present with multiple and simultaneously occurring HP disorders at the time of tumor diagnosis or shortly after surgery. In contrast, patients with radiation-induced dysfunction are diagnosed with one or multiple HP disorders often sequentially and over a period of time extending from a few months to several decades (4, 11, 12). Central diabetes insipidus, a common and challenging complication of tumors or surgical resections involving the HP region, does not occur as a late-effect; it will therefore not be discussed in the present summary (4). The risk of radiation-related HP axis dysfunction increases with the dose of radiation and the duration of follow-up (12). In a study of 748 adult CCS exposed to cranial radiotherapy (CRT) and followed for a mean 27.3 years, the prevalence of having one HP disorder was 51.4% and that of having more than one disorder approached 11% (Fig. 1) (12). Changes in the delivery of radiation, such as the use of proton radiotherapy, may modify the risk or the latency period for the onset of HP axis dysfunction (13, 14, 15).

Figure 1

Relative proportions and overlap among anterior pituitary deficiencies following cranial radiotherapy. Reproduced with permission from Chemaitilly et al. 2015 (12) (©American Society of Clinical Oncology)

Similarly, the mechanisms and lasting influence of novel targeted chemotherapy agents have yet to be fully elucidated (8, 10). Information on the screening and management of HP disorders is summarized in Table 1.

GHD

Prevalence and risk factors

GHD is the most common, and often only, HP disorder observed in survivors of CNS tumors and those whose HP region was exposed to radiotherapy (11, 12). With a prevalence of 12.5%, GHD is the most common endocrine disorder in childhood CNS survivors even after the exclusion of patients with HP tumors (4). The prevalence is even higher in patients exposed to high-dose CRT; for example, the cumulative incidence of GHD exceeded 90% at 4 years of follow-up after the treatment of medulloblastoma (11).

The highest risk factors include tumor growth or surgery within or near the HP region, and HP radiation doses ≥ 18 Gy (4, 12, 16). Patients exposed to 10–18 Gy may also develop GHD if followed for an extended period as the risk increases in a both dose- and time-dependent fashion (17). Patients with HP exposure to radiotherapy for other reasons than CNS tumors, such as acute lymphoblastic leukemia (ALL) with CNS involvement requiring CRT or historic cases where this was done prophylactically (18, 19, 20), diseases requiring hematopoietic stem-cell transplant (HSCT) after conditioning with total body

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Table 1 Risk factors and management guidelines of endocrine late effects: central/hypothalamic–pituitary disorders.

	GH deficiency (child)	Central precocious puberty	TSH deficiency	LH/FSH deficiency	ACTH deficiency
Risk factors					
Primary disease	Tumor or surgery near HP region	Tumor near HP region, optic pathways glioma, neurofibromatosis type 1 Hydrocephalus	Tumor or surgery near HP region	Tumor or surgery near HP region	Tumor or surgery near HP region
Radiotherapy dose to HP region	≥18 Gy TBI ≥10 Gy 1 fraction or ≥12 Gy multiple fractions	≥18 Gy	≥30 Gy	≥30 Gy	≥30 Gy
Other	Young age at diagnosis Tyrosine kinase inhibitors (imatinib) Anti-CTLA4 monoclonal antibody (ipilimumab)	Young age at diagnosis Female sex	Anti-CTLA4 monoclonal antibody (ipilimumab)	Anti-CTLA4 monoclonal antibody (ipilimumab)	Anti-CTLA4 monoclonal antibody (ipilimumab)
Screening modality					
History-main complaints	Decreased growth/ change in clothing sizes	Increased growth/ change in clothing sizes	Slow growth, weight gain, cold intolerance, constipation, menstrual irregularities	Absent or arrested puberty	Decreased energy level
Physical examination findings	Nutrition Auxological measurements Growth velocity Sitting height or upper to lower segment ratio* Pubertal staging**	Nutrition Pubertal changes Auxological measurements Growth velocity Sitting height or upper to lower segment ratio* Pubertal staging**	Auxological measurements Growth velocity Palpation of the neck Pubertal staging**	Amenorrhea Decreased stamina Auxological measurements Growth velocity Pubertal staging**	Auxological measurements Blood pressure
Laboratory screening-plasma levels	–	Morning LH, FSH, testosterone (male) or estradiol (female) if pubertal signs**	FreeT4, TSH	Morning LH, FSH, and estradiol (females) or testosterone (males) if no puberty by age 13 years in girls and 14 years in boys; or if arrest in pubertal development	08:00 h cortisol
Minimal frequency of screening	Clinical examination every 6 months until final height is attained	Clinical examination every 6 months until age 9 years in girls and 10 years in boys Labs as clinically indicated	Clinical examination every 6 months until final height is attained, yearly thereafter Yearly labs	Clinical examination every 6 months until final height is attained, yearly thereafter Yearly labs	Yearly

(Continued)

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Table 1 Continued

	GH deficiency (child)	Central precocious puberty	TSH deficiency	LH/FSH deficiency	ACTH deficiency
Subsequent/confirmatory testing					
Laboratory-plasma levels	GH dynamic testing	LH, FSH, and estradiol (females) or morning testosterone (males) GnRH or GnRH agonist testing	–	Males: repeat morning testosterone	ACTH stimulation test
Radiology/imaging	X-ray of left hand (bone age)	X-ray of left hand (bone age) Consider pelvic ultrasound (girls)	–	–	–
Treatment					
Medications	Replacement with hGH	GnRH agonists	Levothyroxine	Sex-hormone replacement therapy	Hydrocortisone
Additional recommendations	Central precocious puberty may alter growth patterns	GH deficiency frequently appears around the same time	Assess for ACTH deficiency and treat it first	Consider reproductive endocrinology consult when older	Educate on stress doses and emergency situations

*If exposed to spinal radiotherapy or surgery; **males treated with testicular irradiation or alkylating agents may have smaller testicular size than expected for pubertal status. Screening guidelines were adapted from the Children's Oncology Group Long-Term Follow-Up Guidelines Version 4.0 (www.survivorshipguidelines.org).

HP, hypothalamus/pituitary; GnRH, gonadotropin releasing hormone; hGH, human recombinant GH; TBI, total body irradiation.

irradiation (TBI) (21, 22, 23, 24, 25, 26, 27) or non-brain solid tumors of the head such as retinoblastoma (28, 29), nasopharyngeal carcinoma (30) or soft-tissue/rhabdomyosarcoma (31) of the head are all at a risk of developing GHD as a late-effect. Young age at exposure to radiotherapy is an additional risk factor (12, 20, 32).

GHD has been described in a small number of patients treated with conventional chemotherapy alone (5, 6, 7) and may also occur following treatment with targeted chemotherapy agents. Children treated for chronic myelogenous leukemia with imatinib mesylate, a TKI, may experience linear growth deceleration or arrest, but whether this side effect is related to GHD, resistance to GH or direct skeletal toxicity remains unclear (9, 33, 34). Ipilimumab, an anti-CTLA4 monoclonal antibody that is increasingly used to treat unresectable melanoma has been associated with hypophysitis and GHD, possibly persisting after the discontinuation of therapy (10).

Diagnosis and management

GH-deficient children and adolescents usually present with decreased linear growth velocity with sex- and age-adjusted values <-2 s.d. over one year or <-1.5 s.d. over 2 years. Patients with untreated GHD eventually develop short stature (height <-2 s.d.), and medical providers should ideally not wait for this advanced stage

to initiate referrals or investigations (35). Growth failure is frequently multifactorial in CCS and may involve the direct effects on the growth plates of certain therapies such as retinoic acid for the treatment of neuroblastoma (36), nutritional causes and other chronic illnesses. Particular attention should be paid to body proportions and pubertal stage as these can confound or delay the diagnosis of GHD. Vertebral growth plate damage from spinal radiotherapy and complications related to spinal surgery and/or scoliosis can affect the growth of the spine more severely than that of the extremities; the impact of these situations on a patient's stature can be assessed by measuring and monitoring the sitting height (or upper-to-lower segment ratio) (37). Patients who experience GHD and CPP simultaneously may maintain over a period of time a seemingly normal linear growth velocity due to sex steroids increasing GH secretion and inducing local growth factors in the bone (38, 39, 40). Because of rapid fusion of the growth plates under the action of sex steroids, this situation can potentially cause irreversible losses in final height if both conditions are not rapidly detected and treated (41). Linear growth, GH secretion and skeletal maturation may also be influenced by obesity (42).

The diagnosis of GHD in CCS requires a good understanding of the limitations of laboratory testing modalities in this population. Insulin-like growth factor

(IGF)-1 and IGF-binding protein 3 (IGFBP-3) levels may not be accurate surrogate markers in CCS (43, 44). Although failing one stimulation test (and not two as in the general population) is felt to be enough for the diagnosis in CCS with tumors or radiation involving the HP region due to high pre-test probability (35), GH stimulation tests may not always be reliable (45). GH-releasing hormone should not be used for dynamic testing in CCS treated with CRT given the risk of a falsely negative result due to the likely hypothalamic origin of GHD in this population (46, 47, 48, 49). Skeletal maturation should be assessed using a bone age X-ray (50).

Replacement with human recombinant GH (hGH) allows CCS to improve their height prospects, but patients may not entirely recover their adult height potential (based on pre-treatment height prediction or mid-parental height) because of other factors such as skeletal/spinal sequelae, abnormal pubertal timing, chronic illness and primary disease burden. (21, 24, 51, 52, 53, 54) Pro-mitogenic and proliferative *in vitro* properties of GH and IGF-1 have raised concerns regarding the safety of hGH in CCS (55, 56). Long-term follow-up data do not support increased risks of mortality or cancer recurrence in CCS treated with hGH (57, 58). Treatment with hGH was associated with a higher risk of second neoplasms, mostly meningioma (itself a known complication of CRT), in two reports from a large multi-center Childhood Cancer Survivor Study (CCSS) (57, 58). These findings were not replicated by studies from other cohorts (59) or by a more recent report from the CCSS focusing on second CNS neoplasms (60). Treatment with hGH is generally offered one year after the completion of cancer treatments in GH-deficient children in the absence of active neoplasia (56). There are no specific guidelines regarding the observation time needed in children treated for non-malignant CNS tumors such as craniopharyngioma (56). Over the past two decades, the use of hGH has been extended to GH-deficient adults, given the possible benefits on lipids, bone mass, body composition and quality of life (61, 62). However, there are no studies demonstrating a lasting benefit of treating GHD specifically in adult CCS (12).

CPP

Prevalence and risk factors

CPP is defined by the onset of pubertal development as a result of the premature activation of the HP–gonadal axis before the ages of 8 or 9 years in girls and boys respectively (63, 64). Children with tumors located near

the hypothalamus and optic pathways such as low-grade gliomas (with or without neurofibromatosis type 1) and with HP exposure to radiotherapy at doses 18–50 Gy are at risk of developing CPP (54, 65, 66). CPP has also been reported, albeit less frequently, in children treated with CRT for acute leukemia, non-brain solid tumors of the head (32, 54) and in survivors treated with TBI for HSCT (67). The prevalence of CPP in CNS tumor survivors has been reported at 12.2–15.2% (4, 54) and is even higher in patients with tumors located in the HP region (26–29%) (54, 65). Hydrocephalus (4, 65, 66), young age at CNS radiation (<5 years) (68, 69), female sex and increased BMI (68) are additional risk factors.

Diagnosis and management

The diagnostic approach to CPP in CCS is similar to that used in the general population (64, 70). Clinicians should nevertheless be aware of certain features that are specific to CCS (71). Testicular volume may not accurately reflect the pubertal stage of boys treated with gonadotoxic modalities (high-dose alkylating agents or direct testicular radiotherapy); treatment-induced germ cell and Sertoli cell injury may result in small testicular size without impairing testosterone secretion in these patients (72, 73, 74). Scrotal thinning, penile length and pubarche supplemented by AM testosterone and LH plasma levels may be more reliable indicators (71). The frequent occurrence of CPP and GHD within the same time frame and the possible association with other endocrine late-effects are additional challenges (71). The treatment of CPP in CCS primarily relies on gonadotropin-releasing hormone agonist depot preparations (70). Patients with a history of CPP may experience LH/FSHD as a late-effect of CNS radiotherapy several years later and, paradoxically, require long-term sex hormone replacement therapy (54). Tumor burden and comorbidities may impair a patient's ability to fully recover her/his pre-treatment growth potential: a mean final height loss of 0.9 s.d. was reported in patients with a history of CPP within a cohort of prospectively assessed CCS (54).

LH/FSHD

Prevalence and risk factors

Patients with LH/FSHD experience a deficiency in sex hormone secretion because of insufficient stimulation from the hypothalamus and/or the pituitary. The prevalence in CCS was recently reported at 6.5% overall

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Table 2 Risk factors and management guidelines of endocrine late effects: common primary disorders.					
	Primary hypothyroidism	Thyroid cancer	Leydig cell failure	Oligo- and azoospermia	Obesity, diabetes
Risk factors					
Primary disease	Surgical resection of gland	Cancer predisposition syndrome	Surgical resection of gland	Surgical resection of gland	Tumor or surgery near HP region
External beam radiotherapy	Dose ≥ 10 Gy to the thyroid	Any dose to the thyroid; highest risk at 20–30 Gy	≥ 20 Gy to the testes	Any dose to the testes; highest risk at ≥ 2 Gy	Cranial**, TBI**
Other treatments	Tyrosine kinase inhibitors Immunomodulators RAI ^{131}I -MIBG	Alkylating agents may increase risk ^{131}I -MIBG	Alkylating agents	Alkylating agents	Abdominal** Glucocorticoids
Patient factors at cancer diagnosis	Female sex	Younger age	–	–	Female sex*
Screening modality		Female sex			
History-main complaints	Slow growth, weight gain, cold intolerance, constipation Menstrual history	Neck mass	Pubertal changes	Fertility questions	Changes in weight
Physical examination findings	Auxological measurements Growth velocity Palpation of the neck Pubertal staging Plasma TSH, free T4	Neck palpation to check for thyroid nodule or cervical lymph nodes	Stamina Decreased libido Auxological measurements Growth velocity Pubertal staging	Menstrual history Stamina Auxological measurements Growth velocity Pubertal staging Menstrual history Plasma FSH, estradiol	Lifestyle Polyuria or polydipsia auxological measurements Waist/height ratio Pubertal staging Fasting blood glucose, lipids, HbA1c
Laboratory or radiology/ imaging		Thyroid ultrasound†	LH, FSH, morning testosterone	Semen analysis	Dual energy X-ray absorptiometry

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Minimal frequency of screening	Clinical examination every 6 months until final height is attained; yearly thereafter	Yearly	Clinical examination: after 14 years, every 6 months until final height is attained; yearly thereafter	Per patient request (adults)	Clinical examination: after 13 years, every 6 months until final height is attained yearly thereafter	At initiation of long-term follow-up	Clinical examination: every 6 months until final height is attained then yearly
Subsequent/confirmatory testing	Yearly labs	Yearly labs	Yearly labs		Yearly labs	As clinically indicated thereafter	Yearly labs
Laboratory	–	Ultrasound guided FNAB	Repeat morning testosterone level	–	–	Plasma vitamin D 25	Oral glucose tolerance test**
Treatment Modality	Levothyroxine	Total thyroidectomy ± RAI	Sex-hormone replacement therapy	Prevent with sperm banking	Prevent with mature oocyte cryopreservation	Optimize diet, calcium, vitamin D	Lifestyle modification
Additional recommendations	Assess for ACTH deficiency and treat it first	–	Consider reproductive endocrinology consult when older	Consult with reproductive endocrinologist	Sex hormone replacement therapy Consider gynecology or reproductive endocrinology consult	Exercise	Diet Exercise
						Treat other endocrine deficits	Medications as clinically indicated

*For obesity; **for diabetes mellitus; ***may be related to anterior pituitary hormone deficits; †no consensus regarding the role, timing, and frequency of ultrasound. Guidelines were adapted and modified from the Children's Oncology Group Long-Term Follow-Up Guidelines Version 4.0 (www.survivorshipguidelines.org).

BMD, bone mineral density; FNAB, fine-needle aspiration biopsy; HP, hypothalamus/pituitary; RAI, radioactive iodine; TBI, total body irradiation.

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Table 3 Chemotherapy agents associated with gonadal toxicity.

Most commonly used drugs by category

Alkylating agents and non-classical alkylators

Busulfan
Carmustine (BCNU)
Chlorambucil
Cyclophosphamide
Dacarbazine
Ifosfamide
Lomustine (CCNU)
Mechlorethamine
Melphalan
Procarbazine
Temozolomide
Thiotepa

Heavy metals

Carboplatin
Cisplatin

Adapted from The Children's Oncology Group long-term follow-up guidelines version 4.0 – October 2013. (www.survivorshipguidelines.org).

(75) and 11% among those exposed to CRT (12). The main risk factors are tumor growth, surgery and radiation at doses ≥ 30 Gy affecting the HP region (12, 49). LH/FSHD could also occur as a late-effect of HP irradiation at lower doses with longer follow-up (12). It has also been reported in patients treated with TBI (75) as well as those treated with radiotherapy for non-brain solid tumors of the head (30, 32, 76). Hypophysitis subsequent to the use of ipilimumab may also result in LH/FSHD (10).

Diagnosis and management

Depending on attained pubertal stage at the time of onset of LH/FSHD, CCS may present with pubertal delay, arrested puberty, primary or secondary amenorrhea or sex hormone deprivation symptoms. The diagnosis and management of LH/FSHD in CCS follow the same steps as in the general population. The laboratory diagnosis is based on the measurement of LH, FSH and estradiol (females) or AM testosterone (males) (77, 78). The treatment of LH/FSHD in CCS relies on sex hormone replacement therapy (77, 78, 79, 80, 81).

TSHD

Prevalence and risk factors

The prevalence of TSHD has been reported at 7.5–9.2% in survivors of CNS tumors and those treated with CRT (12). The main risk factors are tumor growth, surgery or radiation at doses ≥ 30 Gy affecting the HP region (4, 12). TSHD could also occur as a late-effect of HP irradiation at

lower doses with longer follow-up (12). 'Hidden' forms of TSHD have been described in HSCT recipients conditioned with TBI (82). The clinical relevance of the subtle laboratory findings upon which these diagnoses were based is questionable (83). TSHD has also been described in a small number of patients treated with radiotherapy for retinoblastoma and other non-brain solid tumors of the head (29, 32, 76). Hypophysitis subsequent to the use of ipilimumab may also result in TSHD (10).

Diagnosis and management

Patients with TSHD may experience symptoms of hypothyroidism. The laboratory diagnosis is based on the observation of plasma-free T4 (FT4) levels below the normal range coinciding with TSH levels that are either low or inappropriately normal (77). The treatment relies on replacement with levothyroxine and follows the same steps as in the general population (77). In contrast to the more common primary hypothyroidism, the adjustment of thyroid replacement in patients with TSHD cannot be guided by TSH levels. Given that CCS with TSHD are frequently at risk of developing other HP axis dysfunctions, screening and treatment for ACTHD should precede thyroid replacement: treatment of hypothyroidism can precipitate patients with undiagnosed adrenal insufficiency into adrenal crisis (77).

ACTHD

Prevalence and risk factors

Patients with ACTHD have decreased cortisol secretion because of insufficient HP stimulation. Mineralocorticoid secretion is not significantly impaired in these patients because it is regulated by a different hormonal pathway, the renin–angiotensin–aldosterone system. The prevalence in CCS with a history of CNS tumors or radiotherapy has been reported at 4–5% (4, 12). Tumoral growth, surgery and radiation doses ≥ 30 Gy involving the HPA region are the main risk factors (12, 49). ACTHD could also occur as a late-effect of HP irradiation at lower doses with longer follow-up (12, 84). A relatively high incidence (24%) of ACTHD was reported in a study of CCS treated with HSCT, but this was likely overestimated by the use of testing modalities that are subject to significant variability (85). ACTHD has also been reported in a small number of CCS treated with radiotherapy for non-brain solid tumors of the head (30, 32, 76). Hypophysitis subsequent to the use of ipilimumab may also result in ACTHD (10).

Diagnosis and management

Patients with ACTHD may experience symptoms of fatigue, a greater vulnerability to infections and, if untreated during an acute stressor, are at risk of shock and severe complications (77). The potential severity of this complication mandates a high index of suspicion and at-risk patients should be screened at least yearly by the measurement of an 08:00h plasma cortisol level: values <83nmol/L (3µg/dL) are suggestive of ACTHD, whereas those >413nmol/L (15µg/dL) allow excluding it as a diagnosis (77). Patients with levels 83–413nmol/L should ideally receive confirmatory dynamic testing such as the low-dose ACTH stimulation test (77, 86). The treatment relies on maintenance oral doses of hydrocortisone and teaching patients/families how to escalate doses and/or use injectable forms in situations of emergency ('stress dosing'). Patients should carry at all times documentation (cards, bracelets etc.) that can inform emergency personnel of their risk of adrenal crisis. Patients who are also at risk of TSHD or primary hypothyroidism should be screened for ACTHD and treated for it before the initiation of thyroid replacement (77).

Hyperprolactinemia

Hyperprolactinemia may affect up to 30% of childhood CNS tumor survivors treated with high-dose CRT (39.6–70.2 Gy, with a mean 53.6 Gy) (49). The main risk factor is radiotherapy at doses ≥50 Gy. Hyperprolactinemia in CCS is rarely symptomatic given that patients treated with such regimens frequently have primary gonadal late-effects as well (87). Symptomatic CCS can be treated similarly to patients in the general population.

Thyroid disorders

Thyroid disorders in CCS include primary hypothyroidism, autoimmune thyroid diseases, hyperthyroidism and thyroid cancer (16). Thyroid complications are among the most common endocrine sequelae in the overall population of CCS (3, 16). The risk of developing primary thyroid disease was significantly higher in survivors than that in sibling controls regardless of exposure to high-risk treatments, such as neck radiotherapy, in a recent report from the CCSS (16). Information on the screening and management of thyroid disorders is summarized in Table 2.

Primary hypothyroidism

Prevalence and risk factors

Primary hypothyroidism is one of the most common endocrine late-effects reported in CCS (3, 16, 88). Its overall prevalence among adult CCS has been reported at 13.8–20.8% (3, 89). One of the highest rates is in survivors of pediatric Hodgkin lymphoma, where up to 50% experienced hypothyroidism at 20 years from diagnosis after thyroid exposure to radiation doses ≥45 Gy (88). The prevalence of hypothyroidism in patients treated with HSCT was reported between 14% and 52% (90, 91, 92, 93). Its cumulative incidence among CCS of embryonal tumors of the CNS treated with cranial and cranio-spinal irradiation was 65±7% by 4 years of follow-up (11). With a prevalence of 10%, primary hypothyroidism is also among the most common endocrine complications reported in survivors of malignant extra-cranial solid tumors (76).

The main risk factor of primary hypothyroidism in CCS is the exposure of the thyroid gland to radiation; the risk increases in both a time- and dose-dependent fashion (16, 88). Patients with Hodgkin lymphoma receiving radiation to areas including the thyroid gland (such as mantle fields) represent a high-risk group (88). Female sex and longer durations of follow-up are additional risk factors (88). In HSCT recipients, the main risk factor is conditioning with TBI, especially when treatment is delivered in a single fraction (91). Conditioning with chemotherapy alone such as with busulfan and cyclophosphamide may be associated with transient and often compensated forms of hypothyroidism (90, 94). The treatment of neuroblastoma with (131I)-metaiodobenzylguanidine (¹³¹I-MIBG) is a significant risk factor of primary hypothyroidism, which may occur despite prophylaxis with potassium iodide (KI) (95). Primary hypothyroidism has also been reported in patients treated with radiotherapy for nasopharyngeal carcinoma, retinoblastoma, rhabdomyosarcoma and other extra-cranial solid tumors of the head and neck (29, 30, 32, 76). Treatment with TKIs such as sorafenib, sunitinib and imatinib has been associated with primary hypothyroidism. Possible mechanisms include inflammation, changes in iodine uptake or in the capillary vascularization of the thyroid (8, 96).

Diagnosis and management

Patients at risk for primary hypothyroidism after exposure to radiotherapy should be screened for this condition at least yearly (more frequently during childhood) by

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measuring plasma levels of FT4 and TSH. Patients on maintenance chemotherapy with TKI should also be screened at regular intervals (8). Treatment with levothyroxine may be justified in compensated states (patients with elevated TSH and normal FT4 plasma levels) in patients with a history of neck irradiation because of the trophic effect of TSH on thyroid epithelial cells and the potential association between chronic TSH elevation and thyroid neoplasia (97). The treatment of compensated forms in patients on TKI remains controversial (8). Plasma levels of TSH should be carefully interpreted in CCS treated for primary hypothyroidism after craniospinal radiotherapy. These patients can develop superimposed TSHD over time and have declining TSH values despite being on adequate doses of replacement; the titration of levothyroxine in this situation should primarily be guided by FT4 levels (77). Patients who are at risk of ACTHD (following cranio-spinal radiotherapy for e.g.) should be screened for this condition and treated with hydrocortisone prior to the initiation of thyroid replacement (77).

Autoimmune thyroid diseases

A small number of patients treated with HSCT were reported to develop autoimmune thyroid disease, most likely because of the transfer of abnormal T or B lymphocyte clones from the graft donor to the transplant recipient. These patients may require treatment for primary hypothyroidism, or, less frequently, hyperthyroidism (98). Patients on maintenance chemotherapy with immunomodulators such as pegylated interferon and anti-CTLA4 monoclonal antibodies (for e.g. ipilimumab or bevacizumab) may also develop autoimmune thyroiditis and require treatment for decompensated primary hypothyroidism (10, 96). Patients treated with HSCT should have measurements of FT4 and TSH at least yearly; those with abnormal function tests should get thyroid antibody measurements in order to elucidate the etiology. Screening by measuring plasma thyroid auto-antibodies, FT4 and TSH levels should be offered to patients treated with immunomodulators upon protocol initiation and FT4 and TSH levels should regularly be repeated thereafter (10).

Hyperthyroidism

Hyperthyroidism has been reported in CNS tumor survivors treated with cranio-spinal radiotherapy, in the context of HSCT-induced autoimmune disease, and in

survivors of pediatric Hodgkin lymphoma with thyroid radiation doses >35–40 Gy (16, 88, 98). Management follows a similar approach to that utilized in the general population with the understanding that hyperthyroidism is frequently transient in CCS, and patients may develop primary hypothyroidism subsequently in many instances (98).

Thyroid cancer

Prevalence and risk factors

Thyroid cancer is one of the most common subsequent malignancies experienced by CCS; it is a source of significant concern to survivors whose treatments resulted in thyroid exposure to direct or scatter radiation (16). Thyroid cancer was diagnosed 18.4 times more than expected in survivors of pediatric Hodgkin lymphoma who were treated with radiotherapy (88). In this population, the risk follows an inverted U-shaped curve; it increases with radiotherapy doses up to 20–30 Gy and then decreases again at higher doses likely because of the ablation of the thyroid gland (99). Treatment for a primary cancer before 10 years of age (88) and exposure to alkylating agents (100) were additional risk factors. Secondary thyroid cancer has also been reported in survivors of medulloblastoma treated with cranio-spinal radiotherapy (101), patients conditioned with TBI for HSCT (102, 103, 104), survivors of ALL treated with CRT (103, 105, 106, 107, 108), patients treated with ¹³¹I-MIBG for neuroblastoma despite prophylaxis with KI (109) and those treated with radiotherapy for non-brain solid tumors of the head and neck (32, 110).

Diagnosis and management

Screening modalities for thyroid cancer in at-risk CCS are subject to controversy. False-positive results from ultrasound studies may trigger anxiety and unnecessary additional procedures (103). Some authors argue that these issues may outweigh the hypothetical benefits of an earlier diagnosis obtained via ultrasound when compared to what can be accomplished through a careful yearly clinical examination of the neck by an experienced provider (103). Others have favored using ultrasound and postulated that it will result in diagnosing the disease at a less advanced stage and hence decrease the need for invasive treatments (111). Expert panels have neither discouraged nor explicitly endorsed screening via ultrasound (112). The diagnosis and management of

secondary thyroid cancer in CCS follows the same steps as that of primary thyroid cancer in the general population (112, 113).

Primary testicular disorders

The testes have two distinct functional compartments that show different degrees of vulnerability to cancer treatments; a sex hormone-producing compartment comprising the Leydig cells and a reproductive compartment that includes the germ cells and their supporting system (such as the Sertoli cells). Although both compartments may be damaged by alkylating agents (Table 3) and radiotherapy, Leydig cells tend to be resilient to these treatments in comparison to the germ cells (81). The result of this differential vulnerability is a commonly observed phenotype in male CCS exposed to high-dose chemotherapy, many of whom are able to achieve complete virilization owing to normal Leydig cell function and yet have small testes because of Sertoli cell injury and germ cell depletion; medical care providers should be familiar with this presentation (71). Information on the screening and management of primary testicular disorders is summarized in Table 2.

Leydig cell failure

Prevalence and risk factors

The prevalence of Leydig cell failure among patients exposed to high-risk therapies (alkylating agents or radiation potentially affecting the male reproductive system) has been reported at 11.5–13.3% in adult CCS followed long term (3, 89). The prevalence of Leydig cell failure among CCS treated with alkylating agents was reported at 10–57%, but it was subclinical in the vast majority of cases (normal testosterone values with elevated LH) and rarely required treatment (114, 115, 116). In contrast, up to 80% of male survivors of ALL treated with radiotherapy for testicular relapse with doses >20 Gy to the testes have been reported to require treatment with testosterone (117). Leydig cell failure was reported in CNS tumor survivors after treatment with high-dose alkylating agents, but it does not seem to occur as a result of scatter radiation from cranio-spinal radiotherapy (118, 119, 120). Male CCS treated with HSCT are generally able to retain normal Leydig cell function if they were conditioned for transplant using standard doses of cyclophosphamide or TBI if the cumulative testicular radiotherapy dose was <20 Gy (7, 72, 90, 94, 121). Leydig cell failure has

also been reported in survivors of pediatric Hodgkin's lymphoma (122) and of various solid tumors (76, 123) due to treatment with high-dose alkylating agents and/or testicular exposure to radiotherapy.

Diagnosis and management

Similar to patients with LH/FSHD, patients with Leydig cell failure may experience pubertal delay, arrested puberty or symptoms associated with low testosterone levels depending on the attained pubertal stage at the time of presentation. The diagnosis is suggested by AM plasma testosterone levels that are below the normal range (adjusted to age) contrasting with elevated LH values (124, 125). The management is similar to guidelines available for the general population (79, 124).

Male germ cell failure (oligospermia and azoospermia)

Prevalence and risk factors

Male germ cell failure with resulting infertility due to primary gonadal injury from alkylating agent chemotherapy or radiotherapy is among the most common complications reported in male CCS (81). The prevalence of male germ cell failure was reported at 42.2 (3) and 66.4% (89) in survivors tested with hormonal measurements (FSH and inhibin B) (3) and semen analysis (89) respectively. The risk is significant in all CCS exposed to alkylating agents or other gonadotoxic agents (Table 3) or any dose of radiotherapy to the testes – even as low as 0.15 Gy (126). High-risk groups include HSCT survivors conditioned with cyclophosphamide (especially at cumulative doses >200 mg/kg) and busulfan or TBI (127, 128, 129, 130), ALL survivors treated with alkylating agents at cyclophosphamide equivalent doses ≥ 4000 mg/m² or testicular radiotherapy (126, 131, 132), pediatric Hodgkin lymphoma survivors treated with alkylating agents and/or infra-diaphragmatic radiotherapy (122, 133) and survivors of CNS (118, 119) and other solid tumors (29, 76, 134, 135, 136, 137) with these treatment exposures. Data on the potential effects of targeted chemotherapy agents on male fertility are limited (138, 139, 140).

Diagnosis and management

The limited accuracy of indirect hormonal markers such as plasma levels of FSH and inhibin B mandates the performance of a semen analysis for the diagnosis of male

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germ cell failure (141). Whenever feasible, sperm banking should be offered to male patients prior to treatment with potentially gonadotoxic regimens (81).

Primary ovarian insufficiency

There is a strong interdependence between the viability of the oocyte and the integrity of the hormone-producing granulosa cells in the ovarian follicle (142). The ovaries do not have the functional dichotomy with distinct endocrine/reproductive compartments as seen in the testes, and primary ovarian insufficiency (POI) is the generally accepted term to designate estrogen deficiency and expected fertility impairment due to direct ovarian damage (142, 143).

Prevalence and risk factors

Ovarian function is vulnerable to gonadotoxic chemotherapy drugs such as alkylating agents (Table 3) and radiotherapy (80, 142, 143). Given the age-related natural decline of follicular reserve, older age at treatment exposure has also been described as an additional risk factor (142, 144). The prevalence of POI was reported at 11.8% among female CCS exposed to these high-risk therapies (89). Survivors of CNS tumors may experience POI because of treatment with alkylating agents and ovarian exposure to radiation after cranio-spinal radiotherapy (119, 145). Up to 25.8% of females surviving medulloblastoma experienced POI; this is a likely underestimate given the young age (median age 16.6 years) of this cohort (87, 146). Patients treated with HSCT were reported to experience POI at even higher rates (84%) (147). The majority of female CCS conditioned for HSCT with cyclophosphamide and busulfan experience POI (94, 98). Reduced intensity conditioning regimens using melphalan seem to be less damaging to the ovaries, but long-term data are lacking (148). The risk of POI after TBI seems to primarily depend on age at exposure to radiotherapy: 50% of female CCS treated before the age of 10 years were reported to enter and complete puberty spontaneously while nearly all of those exposed after 10 years of age were diagnosed with POI (149, 150, 151). Even with spontaneous puberty and/or normal progression of development, premature menopause may still occur. Women having normal menstrual cycles and those able to become pregnant despite a history of exposure to TBI experience high rates of miscarriage that

have been attributed to adverse effects on the uterus and/or its blood supply (130, 152, 153). Female survivors of ALL treated with contemporary chemotherapy regimens have been reported to generally be able to experience normal pubertal development but long-term data on fertility are limited (154, 155). Female survivors of pediatric Hodgkin lymphoma may experience POI because of treatment with alkylating agents and/or pelvic irradiation (122, 156); the risk increases with age at treatment (144) and may be lower in patients who had oophoropexy prior to radiotherapy (80) and those treated with chemotherapy alone (157). As with other CCS, female survivors of malignant extracranial solid tumors may experience POI because of the exposure to gonadotoxic chemotherapy or radiotherapy (29, 30, 32, 137, 158, 159, 160). More recently, ¹³¹I-MIBG for neuroblastoma was also reported to be a risk factor of POI (161). Data on fertility outcomes off-therapy and long-term for novel targeted chemotherapy agents are limited (8, 140).

Diagnosis and management

Young pubertal CCS at risk of POI can be offered fertility preservation, preferably prior to cancer treatment, via mature oocyte cryopreservation, a technique that is no longer deemed experimental (142, 162). Depending on the attained pubertal stage at the time of cancer diagnosis, patients with POI may present with delayed puberty, interrupted puberty, primary or secondary amenorrhea or premature menopause (i.e. before 40 years of age) (80, 146). Patients undergoing cancer treatments frequently experience interruptions in their pubertal development or amenorrhea; assessments of ovarian function are generally initiated if such dysfunctions last for more than 2 years after the completion of therapy (163). The laboratory diagnosis is primarily based on the observation of abnormally elevated FSH levels contrasting with low estradiol concentrations (143). The role of other markers of follicular reserve such as antral follicle count via ultrasound and plasma anti-Müllerian hormone levels is yet to be determined in CCS (143). Sex hormone replacement is the mainstay of POI treatment; it aims at inducing pubertal development during childhood and adolescence and promoting skeletal, cardiovascular, psychological and sexual health during adulthood (143). It follows the same guidelines as in the general population (79, 80, 143). Information on screening and management is summarized in Table 2.

Decreased BMD

Prevalence and risk factors

The prevalence of decreased BMD in CCS was reported at 13–18% in long-term CCS (3). Up to 70% of children with leukemia present with disease-related skeletal abnormalities such as fractures and severe BMD deficit (BMD z-score ≤ -2) at the time of cancer diagnosis (164). Prolonged treatment with high-dose glucocorticoids in children with ALL may also result in acute complications such as vertebral body compression fractures and avascular necrosis of the bones (165, 166). Skeletal recovery was noted to begin shortly after the completion of ALL treatments, but BMD may remain abnormally low for age over several years depending on a variety of factors such as the severity of the deficit at baseline, the presence of other chronic health issues and lifestyle variables (165, 166, 167). The prevalence of severe BMD deficit in HSCT survivors has been reported at 19–21% one to 5 years after the completion of therapy (168, 169). Patients treated with HSCT may experience decreased BMD because of the direct effect of leukemia on bone structure or because of treatments such as glucocorticoids and various medical complications related to transplant (168, 169, 170, 171, 172, 173, 174, 175, 176). Additional risk factors include treatment with TBI (172) and/or prior exposure to CRT (177), young age at transplant (178) and a history of GHD (172) and/or sex hormone deficiency (173). Survivors of CNS tumors may experience decreased BMD because of treatment toxicity (glucocorticoids), and GH and/or sex hormone deficiencies as well as sedentary lifestyle (179, 180). Changes in bone remodeling and secondary hyperparathyroidism have been recently described in patients treated with TKI (8).

Diagnosis and management

Patients at risk of decreased BMD may be screened by using dual x-ray absorptiometry (DXA) upon entry to long-term follow-up and as clinically indicated thereafter (89). Interpretation of DXA may be confounded by pubertal delay or short stature (166). There are no specific management guidelines for low BMD in CCS; patients with hormonal deficiencies including vitamin D deficiency should be adequately treated and individuals should be educated on nutritional sources of calcium, the benefits of regular physical activity and the deleterious effects of smoking/alcohol consumption (181). Information on screening and management is summarized in Table 2.

Obesity and diabetes mellitus

Prevalence and risk factors

The risks of obesity (relative risk, 1.8; 95% CI, 1.7 to 2.0) and diabetes mellitus (relative risk, 1.9; 95% CI, 1.6 to 2.4) were significantly higher in survivors when compared to siblings in the CCSS cohort (16). High-risk groups include CNS tumor survivors with a history of HP tumor or surgery; they may experience rapid weight gain and ‘hypothalamic’ forms of obesity that are difficult to control (182, 183). The prevalence of obesity in patients with craniopharyngioma was reported at 55% despite the adequate replacement of all pituitary hormone deficiencies (183). Obesity also affects a substantial proportion of ALL survivors with a prevalence of 34–46% at 10 years of follow-up (184). Although cranial irradiation represents a significant risk factor of obesity and diabetes mellitus in ALL survivors (185), those treated with chemotherapy alone continue to experience high rates of persistent obesity and overweight after many years of follow-up, likely because of their prolonged exposure to high-dose glucocorticoids (186). Patients treated with HSCT do not seem to experience higher rates of obesity than similar aged individuals from the general population, but they were reported to have increased risks of insulin resistance, glucose intolerance and abnormal body composition (187). Diabetes mellitus was reported to affect 5% of HSCT recipients at a median 11 years after transplant (188). Insulin resistance was reported in as many as 52% of long-term HSCT survivors (189). Diabetes and insulin resistance do not seem to be related to obesity, as measured by BMI, in this population (190, 191); their pathophysiology seems to involve abnormal body fat distribution and possibly pancreatic islet cell injury due to TBI (192, 193). Survivors of solid tumors requiring treatment with abdominal radiotherapy may also have a higher risk of glucose intolerance and diabetes mellitus (76, 194, 195, 196, 197).

Diagnosis and management

Screening every 6–12 months for overweight and obesity can be performed using weight, height and BMI measurements with subsequent testing for cardiovascular risk factors following the guidelines in place for the general population. Survivors treated with TBI need to be screened for diabetes mellitus using fasting blood glucose levels at least every two years regardless of whether they are obese or overweight (198). Management of obesity and diabetes mellitus in CCS follows similar steps as in

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the general population. Treatments of hypothalamic obesity have included octreotide (199), diazoxide (200, 201) amphetamine derivatives (202) and more recently glucagon-like peptide 1 receptor agonists such as exenatide (203); data supporting the long-term efficacy and safety of these medications are limited (204). Information on screening and management is summarized in Table 2.

Conclusion

Endocrine complications are among the most prevalent late-effects in CCS. A systematic screening approach should facilitate the early diagnosis and treatment of these conditions and hopefully improve health outcomes. Endocrine late-effects may continue to appear years to decades after the completion of cancer treatments; the importance of long-term follow-up cannot be overemphasized.

Declaration of interest

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