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Endocrine Late Effects of Radiation Therapy in Pediatric and Young Adult Patients with Brain Tumors

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ABSTRACT

With the improvement of treatment techniques, the survival rate for childhood and young adults with brain tumors has increased over the last 40 years. Endocrine late effects account for a large portion of the negative consequences in childhood brain tumor survivors. Treatment of childhood and young adult brain tumors, including radiation therapy, surgery, chemotherapy and other therapeutic techniques often results in endocrine late effects manifested by hypopituitarism, which can involve growth hormone deficiency, hypothyroidism, adrenal insufficiency, gonad disorders, diabetes insipidus, and metabolic complications.

A literature search was conducted on Medline including longitudinal controlled studies, retrospective cohort studies, systematic reviews, recent evidence-based guidelines, meta-analyses, and case reports. An updated review of the latest results and analyses was provided on radiation-induced endocrine sequelae of brain tumor survivors in children and young adults.

Endocrine late effects can occur many years after the initial radiation treatment of a brain tumor, so surveillance of growth, weight, puberty, bone age development, and endocrine status is recommended every 6 months to 2 years after tumor therapy. Pediatric and young adult survivors with brain tumors are important follow-up subjects. Early diagnosis and appropriate treatment may improve health outcomes. Newer radiation treatment techniques, such as proton radiotherapy, can reduce endocrine complications, but this benefit has not been proven as additional research is needed on short-term and long-term results.

Keywords: Radiotherapy, normal tissue toxicities, childhood cancer, intracranial tumor, radiation-induced hypopituitarism

INTRODUCTION

The incidence rate of overall cancer among children 1-14 years of age is about 140.6 per million and 155.8 per million in those aged 15–19 years [1, 2]. Cancer is the second most common cause of death among children aged 1-14 years in the United States, surpassed only by accidental deaths

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[3]. Malignant brain tumors are the second most common cancer in children (accounting for 21% of all pediatric cancers) and the third most common cancer in adolescents (accounting for 10% of all adolescents cancers) [4]. Low grade gliomas (LGG) account for 35% of children diagnosed with central nervous system (CNS) cancers [2]. Many possible variables such as genetic, immunological, or environmental factors (electromagnetic fields, ionizing radiation, pesticides, etc.) may be related to the development of cancer in children. Changes in personal mobility over the past decades, changes in exposure to artificial and natural substances, and changes in social structure (family size, changes in breastfeeding and immunity attitudes), could play a role in the development of childhood cancer [2].

Over the past 40 years, the possibility of rehabilitation for children and adolescents affected by tumors has steadily increased due to the continuous improvement of treatment options, and considering all types of childhood tumors, the current recovery rate is about 80% [5]. Surviving patients may continue to experience delayed chronic health conditions for months to decades after treatment of the primary cancer; this condition is called late-effects [6]. Incidence damages the proportion of treatment-related sequelae in cancer survivors, and the cumulative incidence of various endocrine gland dysfunctions continues to rise [6]. These increased risks are associated with multiple chemotherapeutic drugs, tumors located near the Willis ring, and brain irradiation.

A Japanese study included 122 survivors diagnosed with various cancers, 67% of which had endocrine problems [7]. As the long-term survival outcomes in these children improved, the late effects of treatment became important factors related to quality of life and medical expenditures [8]. Radiation therapy (RT), surgical resection, alkylating agent chemotherapy, immunotherapy and other treatment modalities all contribute to endocrine sequelae, including hypothalamic-pituitary axis (HPA) dysfunction, endocrine end organs, the thyroid gland and gonads, as well as bone and metabolic complications. The risk of anterior pituitary dysfunction in childhood cancer survivors (CCS) treated with transcranial RT increased in a time- and dose-dependent fashion [9,10]. After curative treatment of childhood brain tumors, many survivors will face health-related challenges. Neuroendocrine disorders can play an important role in the long-term health and well-being of CBTS. For children surviving brain tumors, sufficient circulating hormone concentration is essential for normal rehabilitation, puberty development and growth, and optimal daily participation, which underscores the importance of timely monitoring of the complete endocrine system [11].

Although curing brain cancer in children and adults is now a realistic goal, the neuroendocrine consequences of treatment remain a major concern for cancer survivors and clinicians involved in subsequent care. Anterior pituitary hormone deficiency is the most common complication of successful brain cancer treatment in children and adults. This paper aims to provide an overview of the epidemiology and risk factors of radiation-induced endocrine late effects and describes strategies for effective diagnosis and management of patients based on recent developments. For this purpose, a thorough literature search was conducted including longitudinal controlled studies, retrospective cohort studies, systematic reviews, recent evidence-based guidelines, meta-analyses, and case reports. As a result, an updated review of the latest results and analyses was provided on radiation-induced endocrine sequelae of brain tumor survivors in children and young adults.

METHODOLOGY

A search for original articles published after 1980 on hypopituitarism after cancer treatment was performed in MEDLINE and PubMed. The search terms used were “cancer”, "brain tumor”, “pituitary tumors”, “radiation therapy” in combination with “hypopituitarism”, “hypothalamus”, “childhood brain tumors survivors”, “childhood and young adult with brain tumors”, “growth hormone”, “GHRH”, “ACTH”, “TSH” “gonadotropin deficiency”, “hyperprolactinemia”, “growth and/or puberty” “central diabetes insipidus”, “bone mineral density”, “obesity”, “diabetes mellitus” and “metabolic syndrome”. The papers cited in this review were chosen from the reference lists obtained from the search, as well as from the reference lists of the articles obtained as above. All papers identified were English-language, full-text papers.

Radiation-Induced Hypopituitarism

Total radiation dose, the size of the exposed tissue, and the time for tissue repair are closely related to radiation-induced hypopituitarism. The impaired hormone secretion of the hypothalamus-pituitary axis is mainly caused by the direct effect of radiation on the DNA of the hypothalamus and pituitary cells, which causes irreversible damage and leads to hypofunction [12,13]. RT can affect the development of large blood vessels leading to atherosclerosis, thromboembolism, rupture, and aneurysms. In addition, it can cause inflammation of small blood vessels and thrombosis,

leading to ischemic necrosis of peripheral nerve tissue. When exposed to relatively large doses of radiation, blood vessels tend to develop hemorrhage, edema and thrombosis. However, when using lower doses of radiation, the initial vascular damage is not obvious, and is mainly manifested by delayed capillary dilatation and hemorrhagic infarction up until 1 year after radiation exposure [14].

The importance of limiting dose to critical normal structures such as the cranial nerves and nuclei, brainstem, temporal lobes, and optic chiasm has previously been proven. RT involving these structures can also damage the hypothalamus (HT) and pituitary gland (PG), resulting in hormonal failure of the hypothalamus-pituitary axis. This can cause endocrine dysfunction, with obvious symptoms, and often requires life-long hormone replacement therapy [15]. Isolated growth hormone deficiency (GHD) is induced by doses of 18-24Gy [16]. There is a significant relationship between pituitary dysfunction and radiation doses of 30Gy or higher [17]. A dose of 30–50Gy, which is usually used in patients with moderate-risk brain tumors, permanently destroys the gonadotropin, thyrotropin axis and adrenocorticotropic hormone. A dose of >60Gy ("full-dose radiation") will cause panhypopituitarism [16]. These doses can impair other neurocognitive functions and prevent patients from living a normal lifestyle.

A significant correlation between dose to the HPA and tumor location was observed. Comparison of various RT techniques used in medulloblastoma showed that conformal irradiation techniques could achieve better dose distribution of target coverage, lower average pituitary doses, but higher doses for mandible, parotid, pharynx and thyroid gland [18]. Moreover, higher integral doses could lead to a higher risk of radiation-induced tumors [19]. GHD is the most common post-irradiation abnormality among CBTS, followed by gonadotrophin (GT), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH) and pro¬lactin (PRL) disorders [20].

Traditional retinoblastoma RT exposes the pituitary and hypothalamus to large amounts of radiation. Survivors have an increased risk of multiple growth and metabolic defects due to endocrine dysfunction [21]. Proton radiotherapy (PRT) eliminates the midline structure including the hypothalamic-pituitary axis of radiation dose and is, therefore, expected to have a much lower incidence of endocrinopathy. Importantly, PRT allows lower doses to be delivered to the hypothalamic/pituitary axis, teeth, temporomandibular joint, mandible, cochlea, thyroid and posterior temporal lobe compared to the same fields deployment using photons [19]. Therefore, in addition to reducing the risk of radiation-induced malignant tumors, PRT can also reduce the risk of radiation-related endocrine dysfunction [22].

The energy distribution of PRT enables higher planned target volume compliance and reduces doses surrounding the treatment target. Achievement of a high eligibility index indicates that PRT may lead to an increase in dose, thereby avoiding the delivery of a relative biological effectiveness (RBE) equivalent dose of 66.6-77.4Gy to CNS tumors in the brain stem [23]. Compared to traditional photon therapy, reducing low-dose baths to normal tissues surrounding the treatment target is also thought to significantly improve radiation-related toxicity. When utilized for medulloblastoma, PRT craniospinal irradiation (CSI) is thought to reduce long-term endocrine, cardiac, gastrointestinal, and neurocognitive deficits, and a reduction in secondary tumors [23].

PRT has been found to decrease the exposure of normal tissues by 2–3 times for small field exposures and 6-11 times for CSI patients [24]. Reports from the Pediatric Proton Foundation and the National Proton Therapy Association showed that the use of PRT in pediatric patients increased by 36% between 2010 and 2013 [25]. Studies comparing proton and photon cohorts reported that by using PRT, blood and gastrointestinal toxicity were reduced [26], changes in IQ were reduced, and quality of life score increased [27], and patients with cancer treated with PRT were found to be less likely to develop a second type of cancer than patients treated with photon radiation therapy [28]. Recent evidence on the use of PRT in pediatric patients supports its effectiveness and potential benefits to reduce the incidence of severe toxicities in later life [29]. Extensive follow-up of the population of PRT patients is still needed to determine the incidence of late-onset toxicity and secondary malignancies.

Brain Tumors

According to the International Classi¬fication of Childhood Cancer (ICCC), childhood brain tumors (central nervous system and miscellaneous intracranial and intraspinal neoplasms) are mainly divided into five categories: (a) ependymomas and choroid plexus tumor (including ependymomas and choroid plexus tumor); (b) astrocytomas; (c) intracranial and intraspinal embryonal tumors (including medulloblastomas, PNET, medulloepithelioma and atypical teratoid/rhabdoid tumor); (d) other gliomas (including oligodendrogliomas, mixed and unspecified gliomas, neuroepithelial glial tumors of uncertain origin); (e) other specified intracranial and intraspinal neoplasms [1].

The range of tumor types varies significantly with age groups. Among children aged 0 to 14 years in the United States, acute leukemia accounts for 31% of all cases and CNS tumors account for 21%. However, among young people aged 15-19 years, the proportion of leukemia cases is 12%, CNS tumors account for 10% [4]. The highest incidence of all CNS tumors in high-income countries is clearly related to the widespread use of diagnostic facilities. The low incidence in low- and middle-income countries is likely to proportionately reflect poor access to neuroimaging facilities (for example, fewer CT or MRI scanners, longer waiting times, and excessive diagnostic testing costs [4].

Hypothalamic-Pituitary Axis (HPA) Complications

HPA dysfunction includes the following diseases: central GHD, thyroid stimulating hormone deficiency (TSHD), adrenocorticotropic hormone deficiency (ACTHD), luteinizing hormone (LH)/follicle-stimulating hormone (FSH) deficiency (LH/FSHD), precocious puberty, hyperprolactinemia and central diabetes insipidus (DI). Related clinical features of each pituitary hormone deficiency are demonstrated in Table 1.

Table 1: Clinical Manifestations of Hypopituitarism (adapted from Ref. [30])

Symptom/Sign	Pituitary trophic hormone deficiency
General	
Fatigue, weakness	ACTH, TSH, LH/FSH, GH
Weight gain	TSH
Weight loss	ACTH
Decreased exercise capacity	ACTH, TSH, LH/FSH, GH
Impaired sleep quality	TSH, LH/FSH, GH
Depression	TSH, GH, LH/FSH
Skin	
Pallor	ACTH, LH, FSH
Dry skin	ACTH, TSH
Thinning hair, loss of body hair	ACTH, TSH, LH/FSH
Cardiovascular/metabolic	
Hypertension	TSH, GH
Hypotension, particularly orthostatic	ACTH
Bradycardia	TSH
Decreased lean body mass, increased fat mass	GH
Hyperlipidemia	TSH, GH
Insulin resistance, impaired glucose tolerance	TSH, GH
Hypoglycemia	ACTH
Impaired cardiac function	ACTH, TSH, GH
Premature atherosclerosis	TSH, GH
Pulmonary	
Shortness of breath, dyspnea on exertion	ACTH, TSH

Gastrointestinal	
Anorexia	ACTH
Nausea/vomiting	ACTH
Diarrhea/loose stools	ACTH
Constipation	TSH
Musculoskeletal	
Muscle weakness	ACTH, TSH, LH/FSH, GH
Osteoporosis, fractures	ACTH, TSH, LH/FSH, GH
Renal	
Increased thirst	ADH
Polyuria, nocturia	ADH
Reproductive	
Oligo/amenorrhea	ACTH, TSH, LH/FSH
Erectile dysfunction	LH/FSH
Low libido	LH/FSH
Hot flashes	LH/FSH
Infertility	LH/FSH
Vaginal dryness	LH/FSH

When the HPA enters the radiation field, various endocrine disturbances may occur due to its radio-sensitivity. The spectrum damage of the HPA depends on many factors, which are not only related to the parameters of RT (organ/tissue volume, fraction size, total radiation dose), but also to the host (developmental status, gender, age). HPA dysfunction varies depending on the location of the tumor and the treatment. Patients suffering from direct hypothalamic-pituitary (HP) injury with local tumor growth or surgical resection are usually associated with multiple concurrent diseases, tumor diagnosis time, or shortly after surgery. In contrast, patients with radiation dysfunction are often diagnosed with one or more HP disorders from the beginning for a period of months to decades [31]. Radiation-induced anterior pituitary hormone deficiency is progressive and irreversible. Regular testing must be performed to ensure timely diagnosis and early hormone replacement therapy [16].

Growth Hormone Deficiency (GHD)

Prevalence and risk factors

It is estimated that the lifetime prevalence of late endocrine effects of CCS is 50% [6]. Hypothalamic/pituitary (HP) radiation is a major risk factor for GHD, and the prevalence of CCS treated in this manner was reported to be 46.5% [32]. Laughton et al. observed a 4-year cumulative incidence of 94% for a group of children undergoing cranial radiation or craniospinal irradiation for embryonic brain tumors (median doses of the pituitary and hypothalamus were 42.1Gy and 44.0Gy, respectively) [32]. GHD is also radiation dose dependent, with the highest risk after HP radiation being 30Gy. However, there is also a risk with total body irradiation (TBI) at 10Gy (single-fraction) and 12Gy (multiple-fraction). Other risk factors include HP tumor involvement, younger age at diagnosis, and use of tyrosine kinase inhibitors or antibodies targeting the immune checkpoints T-lymphocyte-associated protein 4 (anti-CTLA4 monoclonal antibodies) [33]. The risk of GHD increases in a time-dependent manner, so it increases with the length of follow-up.

The hypothalamic and pituitary components of the hormone axis are susceptible to tumor compression or invasion, and are susceptible to intracranial interventions such as radiation therapy and surgery [34, 35]. Chemotherapy has been reported to enhance the harmful effects of radiation on pituitary function [36, 37]. After a brain tumor is diagnosed, nearly 60% of the patients in the study cohort that survived the childhood brain tumor had impaired growth. Several factors including delayed puberty, lack of sex hormones, and/or hypogonadism have been associated with poor growth. If patients received cranial or craniospinal radiation, or received chemotherapy, their average height was below the target height. Their average height was also lower than

that of patients without these factors [38]. Growth hormone secretion has been shown to be sensitive to radiation damage. In addition, tumor location was statistically significant for reducing growth hormones [39].

Diagnosis and management

The treatment of childhood brain tumors is frequently complicated by growth retardation with a high proportion of irradiation-induced GHD resulting in reduced adult final height (AFH) [40]. It is recognized that short stature is usually the only feature of growth hormone-deficient children and adolescents. An immediate investigation should be initiated according to the following criteria: 1) severe short stature, defined as a height > 3 SD below the mean; 2) a height > 1.5 SD below the mid-parental height; 3) a height > 2 SD below the mean and a height growth rate over 1 year > 1 SD below the mean for chronological age, or a decrease in height SD of > 0.5 over 1 year in children over 2 years of age; 4) in the absence of short stature, a height growth rate > 2 SD below the mean over 1 year or > 1.5 SD sustained over 2 years; this may occur in GHD, presenting in infancy, or in organic acquired GHD; 5) signs of an intra-cranial lesion; 6) signs indicative of MPHD; and 7) neonatal signs and symptoms of GHD [41]. Untreated GHD patients will eventually have short stature (height <-2 SD). Ideally, healthcare providers should not wait for this advanced stage to begin referrals or investigations [46]. Skeletal maturation should be assessed using a bone age x-ray image [42].

Growth failure is usually multifactorial in CBTS and may involve the direct effects of certain therapies, drugs, nutrition, hormones, and other chronic diseases on growth plates. Particular attention should be paid to body proportions and puberty as they can confuse or delay the diagnosis of GHD. Patients who experience both GHD and CPP may maintain a seemingly normal linear growth rate for a period of time, which is caused by sex steroids that increase growth hormone secretion and induce local growth factors in the bone [43]. Due to the rapid fusion of growth plates using sex steroids, if neither condition can be quickly detected and treated, the condition may lead to irreversible loss of final height [10].

Obesity may also affect linear growth, growth hormone secretion, and bone maturation. Increased hypothalamic somatostatin secretion may occur in obese individuals, resulting in secondary reduction of growth hormone secretion. Accelerated clearance of growth hormones in obese children remains unknown. Despite reduced circulating growth hormone levels, plasma IGF-I levels are normal or elevated in obese children [44].

Evidence that prolactin promotes mitosis and DNA synthesis is based on in vitro studies on the proliferation of epithelial cells in the breast tissue of several different species and studies on the division of Nb and node lymphoma cells [45]. However, human prolactin only binds to prolactin receptors to stimulate lactation, and unlike human growth hormone, it does not bind to growth receptors to stimulate bone growth because human prolactin and growth hormone molecules and their respective receptors have only limited homology in structure. When the serum prolactin concentration of a patient is increased after neurosurgery, it is usually only mildly abnormal, so it is unlikely to have a significant effect on the body growth [46].

A single growth hormone measurement is insufficient. The use of other known growth hormone secretagogues (such as L-dopa, clonidine, arginine, or propranolol-glucagon) is also problematic. Historically, the response of growth hormone to insulin resistance tests has been considered the gold standard for the diagnosis of GHD, especially in adult patients. The accepted definition of complete GHD is a peak growth hormone response to insulin-induced hypoglycemia below 3 μg/l. However, there is an inherent risk of hypoglycemia caused by insulin injections. Pediatric brain tumor survivors may have known seizure disorders and have a higher risk of seizure; therefore, the insulin resistance test (ITT) is potentially harmful to these patients [47].

This increase is necessarily independent of the effects of growth hormone and may reflect the regulation of IGF-1 and IGFBP-3 production by gonadal steroids. Precocious puberty usually masks GHD by increasing growth rate, advancing bone age, and normalizing IGF-1 and IGFBP-3 levels, even without normal growth hormone secretion. This could explain the poor predictive value of IGF-I and IGFBP-3 measurements in adult patients with brain tumors and GHD, as well as in early adolescent children [6]. In this population, as puberty progresses, the production of gonadal steroids increases and even in the face of GHD, the IGF-1 and IGFBP-3 concentrations rise to normal levels. Therefore, monitoring GHD in brain tumor survivors depends more on clinical findings, accurate longitudinal nutritional data, and stimulating growth hormone detection rather than on monitoring serum IGF-1 and IGFBP-3 concentrations [48]. Serum levels of IGF-I and IGFBP-3 do not always reflect GHD in children with brain tumors, especially in hypothalamus-chimeric gliomas or children who have reached puberty [48].

Since the late 1950s, human pituitary extracts have been used to treat children with GHD. Growth hormone has been produced by recombinant DNA technology since the 1980s and can be used for a variety of diseases. However, with the increasing amount of human recombinant growth hormone being prescribed, the potential safety issues related to treatment have attracted attention [49]. Replacing with human recombinant growth hormone (rhGH) allows CBTS to improve height prospects, but patients may not fully recover their adult height potential (based on pre-treatment height predictions or parental mid-heights) such as spinal/skeletal sequelae, chronic disease, primary disease and abnormal timing of puberty [40,42]. Growth hormone treatment was previously used conservatively, but is now more commonly used, which is fortunate for patients because of the short height of adults and the risk of GHD-related metabolic consequences. However, once growth is complete and as pediatric patients transition to adulthood, problems arise with the continued need for growth hormone treatment. Adult GHD is associated with poor body composition, lipid distribution, bone mineralization, glucose metabolism and heart function. It is also related to a decline in quality of life and a reduction in lifespan.

The availability of rhGH and its beneficial effects on adult height prospects underscore the importance of diagnosing GHD in these patients [49]. Testing for GHD should begin when growth hormone treatment is considered safe. Therefore, provided the risk of tumor recurrence or second tumor development under rhGH being reasonably low, it is recommended to start rhGH therapy as early after oncology treatment as possible [50, 51,], approximately 1-2 years later, in order to alleviate poor growth outcome in GHD childhood medulloblastoma survivors. When the chance of cancer recurrence is greatest, growth hormone treatment should be avoided for the first 2-3 years after cancer treatment is completed. Although evidence of a causal relationship between rhGH treatment and tumor recurrence is lacking, alternative treatments provided during this period may be unintentionally associated with tumor recurrence and death [51]. The increased risk associated with the use of growth hormone appears to decrease with increasing follow-up time, and the overall risk remains small. This risk should be weighed against the potential benefits of growth hormone treatment for cancer survivors.

During growth hormone treatment, some patients experience arthralgia involving small or large joints, but usually there are no signs of inflammation or exudation, and x-ray examinations do not show abnormalities [52]. These changes are also resolved as the dose is reduced and may be due to swelling of the articular cartilage, although the exact mechanism is unknown. Evidence suggests that growth hormone treatment can lead to hyperinsulinemia, which may increase the risk of cardiovascular complications, and this can be caused by elevated serum lipoprotein(a), also referred to as Lp(a) [53]. Growth hormone-induced hypertension and atrial fibrillation have been reported but rarely occur. Benign intracranial hypertension (BIH) has also been reported to be associated with growth hormone treatment [54]. Most affected patients are children, and BIH improves as treatment ceases [49]. Because growth hormone suppresses the conversion of cortisone to cortisol, patients receiving glucocorticoid replacement may require higher doses once growth hormone is initiated, and those with low adrenal reserve may be rendered hypoadrenal by the growth hormone therapy [30].

Luteinizing Hormone/Follicle-Stimulating Hormone Deficiency (Lh/Fshd)

Prevalence and risk factors

Patients with LH/FSHD have insufficient sex hormone secretion due to insufficient hypothalamic and/or pituitary stimulation. Sex hormone deficiency is statistically significantly associated with tumors located in or near the saddle area and RT treatment. Tumors in 50% of hypo gonadal patients are located in or near the saddle area and nearly 90% of hypogonadal patients receive RT. More than 60% of patients with hypogonadism had received chemotherapy, but the correlation was not statistically significant. Hypergonadism and hypogonadism were found. Patients may have both central and hypogonadism [32]. Vatner et al conducted a cohort analysis, which included over 200 patients treated with PRT. It was found that the 5-year incidence of gonadotropin deficiency was relatively low compared to growth hormone, with an actuarial rate of 14.0% when the mean hypothalamic and pituitary median doses exceeded 40 CGE (Cobalt Gray Equivalent) [55]. Lack of sex hormones, hypogonadism and delayed pubertal induction are associated with growth disorders. For short stature, puberty induction is postponed to ensure better adult height, however, normal height is not reached. Sex hormones play a very important role in both physical and psychological development, and this should be considered when planning the timing of inducing puberty [38]. Due to HPA exposure, early puberty and delayed puberty are

common complications of RT for treating central nervous system tumors in children [56].

Diagnosis and management

The diagnosis and treatment of LH/FSHD in CBTS is the same as in the general population. Laboratory diagnosis is based on measurements of LH, FSH and estradiol (female) or AM testosterone (male) and LH/FSHD treatment-dependent hormone replacement therapy in CCS [57]. Normal or low normal basal LH and/or FSH levels, as well as reduced circulating hormone concentrations and/or decreased fertility, can confirm the diagnosis of gonadotropin deficiency. Gonadotropin deficiency can delay linear growth in children and adolescent development, especially in the case of GHD, which almost always occurs after treatment with radiation doses that cause gonadotropin deficiency. Gonadotropin deficiency is more common in adults than in children and can lead to fatigue, reduced sexual activity, and decreased quality of life [13]. The treatment of LH/FSHD depends mainly on the treatment goals, e.g., it is only for puberty induction or it also aims to induce fertility. The Endocrine Society's clinical practice guidelines recommend testosterone replacement for adult males with central hypogonadism and no contraindications to prevent osteoporosis, fractures, and improve libido, sexual function, energy levels, reduced fat mass, increased muscle mass and strength [30].

Central Precocious Puberty (CPP)

Prevalence and risk factors

CPP is defined as the development of sexual characteristics in boys before the age of 9 and the development of sexual characteristics in girls before the age of 8 due to activation of the hypothalamus ± pituitary ± gonadal axis. The incidence of idiopathic forms and the development pattern of CPP vary by gender [58]. It has been reported that the prevalence of CPP among survivors of CNS tumors is 12.2–15.2% [59], with almost a two-fold increase in CBTS with HPA tumors [60]. In a recent study, the prevalence of CPP was 26% among children with optic glioma [59]. Age at radiation (<5 years), female, high BMI are also risk factors for CPP in CBTS [11,61].

Diagnosis and management

The diagnosis of CPP in CBTS is similar to the numbers used in the general population. Breast development in girls and testicle size 4 mL in boys are the basis for diagnosing adolescence [11]. However, clinicians should pay attention to certain specific functions of CBTS [62]. Penile length, scrotal thinning, and pubarche supplementation with testosterone and LH plasma levels may be more reliable indicators [8]. The treatment of CPP in CBTS relies mainly on gonadotropin-releasing hormone agonist depot preparations. Patients with a history of CPP may experience LH/FSHD after a few years, which are late effects of central nervous system radiation therapy and long-term sex hormone replacement therapy is required [59]. Tumor burden and comorbidities may impair a patient's ability to be fully restored to their pre-treatment growth potential.

Prompt diagnosis of precocious puberty is important, and bone age estimation is a powerful tool for obtaining information about the ultimate height potential. In children receiving radiation therapy, the final height deficiency is usually more severe, because GHD is almost always present, which can lead to a weakened pubertal growth spurt and further loss of growth potential. Precocious puberty may also mask the presence of GHD in some patients and may cause further delay in the diagnosis and initialization of growth hormone replacement therapy [13]. Survivors who experience precocious puberty are more likely to develop hypogonadism in adulthood, which is also related to brain RT doses greater than 30 to 50Gy [56].

Boys with organic CPP associated with central nervous system lesions experience adolescence earlier than those with idiopathic CPP. The LH/FSH peak ratio is lower after the GnRH stimulation test, because partial gonadotropin deficiency may be the result of the lesion and/or its treatment. Although there were no significant differences, girls with organic GPP still had higher LH and FSH peaks and LH/FSH peak ratios after the GnRH stimulation test. This suggests greater activation of the hypothalamus ± pituitary ± gonadal axis in organic CPP, and suggests that girls with idiopathic CPP develop more slowly [11]. Patients with CNS lesions also had higher BMI and leptin concentrations compared to patients with idiopathic CPP. Lesions and/or their treatment may lead to an increase in BMI by damaging the hypothalamic appetite regulation center. Higher plasma leptin concentrations may be due to increased BMI and/or partial resistance to leptin caused by central nervous system disease and/or its treatment as leptin receptors [59]. Since leptin is important in weight regulation, this will further stimulate weight gain. Leptin has been proposed to play an important role in the maturation of hypothalamic-pituitary function [60], including GnRH, FSH secretion and LH. There are reports suggesting, despite the presence of partial gonadotropin deficiency, that these patients are still at risk

for excessive bone age development, and GnRH analogs are recommended for treatment [51, 59].

Thyroid Stimulating Hormone Deficiency (TSHD)

Prevalence and risk factors

The incidence of radiation-induced HT varies widely among various reports, and there is usually limited follow-up. In a study by Tell et al [61], material from patients with non-thyroid head and neck cancer was analyzed for the incidence of HT up to 10 years after RT. The Kaplan-Meier risk for HT at 5 and 10 years after irradiation was 20% and 27%, respectively. The prevalence of TSHD was reported to be 7.5–9.2% in CNS tumor survivors and patients treated with conformal radiation therapy [63]. The main risk factors are tumor growth, location of the tumor and high (>30Gy) radiation dose [11]. The thyroid is the largest pure endocrine gland in humans. The main thyroid hormones (triiodothyronine; T3 and thyroxine; T4) are essential for normal growth and development, total energy expenditure and substrate utilization [64]. As a result, these hormones affect the function of virtually all organ systems. Like the ACTH axis, the HP-thyroid axis appears to be the least susceptible to radiation damage, and any injury that occurs is highly dose-dependent [61]. These sequelae may include primary or central hypothyroidism, thyroiditis, Graves' disease, euthyroid Graves' eye disease, benign adenoma, multiple nodular goiter, and radiation-induced thyroid cancer.

Diagnosis and management

CBTS exposed to the neck or hypothalamus/pituitary region should receive a baseline thyroid function test, including measurements of TSH. Then, at least annually, all individuals with direct or accidental exposure to the thyroid or hypothalamic/pituitary area should be assessed for a history of symptoms of thyroid dysfunction (heat tolerance, skin and hair changes, weight change, activity levels, menstrual symptoms), clinical examination, measuring fT4 (with or without fT3) and TSH. Some authors believe that thyroid function should be assessed 1 month after treatment and then at least 3 to 6 months later up to at least 5 years [65]. Other researchers recommend monitoring 6 months after RT [66]. Measurement of thyroid function should also be mandatory in patients receiving a second head and neck tumor treatment [67]. Measurements of antithyroid peroxidase, anti-thyroglobulin, and thyroid stimulating hormone antibodies can be used to diagnose thyroiditis and other thyroid diseases. However, when new treatment techniques are used, longer follow-up is necessary to assess the risk of thyroid disease caused by radiation therapy. The American Cancer Society has recommended that primary care clinicians should assess thyroid function in head and neck cancer survivors by measuring TSH every 6-12 months.

Recommended follow-up procedures include at least an annual assessment of symptoms of thyroid dysfunction, clinical examinations, and measurement of thyroid hormones and thyroid-stimulating hormones. Normal TSH levels after the TRH stimulation test indicate hypothalamic dysfunction, while non-response to TRH indicates damage to the anterior pituitary. Almost 20-30% of patients receiving RT will develop primary hypothyroidism within 5 years after RT [68]. Treatment of hypothyroidism is based on hormone replacement therapy. Thyroid hormone therapy is also recommended in cases of subclinical hypothyroidism [68]. In addition, Zoberi et al. describes a prospective study design showing that subcutaneous amifostine administered before each RT treatment reduces the long-term incidence of HT in head and neck cancer patients [69]. Given the increasing incidence of patients with advanced radiation-induced HT, life-long TSH screening is recommended after RT to the neck. For patients with hypothyroidism, early thyroid hormone replacement therapy is essential to maintaining the best quality of life for cancer survivors [61].

Adrenocorticotropic Hormone Deficiency (ACTHD)

Prevalence and risk factors

The prevalence of CCS with a history of CNS tumors or RT is reported to be 4–8% [35, 11,70]. Tumor growth, surgery, and radiation doses involving HPA areas ≥30Gy are major risk factors [40]. ACTHD occurs almost completely when hypothalamic and pituitary PRT median doses are ≥40Gy, with a 5-year actuarial rate of 8% [55]. The incidence and severity of ACTHD increases with longer follow-ups after radiation treatments [35]. Among patients having non-pituitary disease, the pituitary-adrenal axis appears to have relative radio resistance, and clinically significant ACTHD is not common in patients with a total radiation dose to the HPA of less than 50Gy (about 3%) [71], and are almost unreported after TBI [72, 73]. Intense exposure (>50Gy) results in a significant increase in the incidence of ACTHD, with a cumulative incidence of 27-35% within 15 years after exposure. However, due to the symptoms of cortisol deficiency, most cases of ACTHD are partial, and only a few patients require regular hydrocortisone replacement therapy [74, 75]. For patients undergoing conventional RT

for pituitary tumors, the incidence of ACTHD has increased significantly to 31-60% [70, 76, 77]. In the absence of ACTHD indicated by normal adrenocortical hormone-induced hypoglycemia response, it is speculated that in addition to the direct effects of radiation, chronic stress related to chronic disability and poor quality of life caused by the treatment may also play a role in this phenomenon [78].

Diagnosis and management

Central ACTHD represents insufficient cortisol secretion due to ACTH deficiency. When ACTH is blocked by pituitary disease, it can be secondary or tertiary to hypothalamic CRH deficiency. A high degree of suspicion is needed to diagnose ACTHD, as delayed treatment can lead to adrenal crisis and death. Mild ACTHD may manifest as clinically important ACTHD with stress [59].

Patients with ACTHD may experience extreme fatigue, decreased appetite, low blood pressure, and even fainting and are more susceptible to infection. If untreated under acute stress, there is a risk of shock and serious complications [30]. The potential severity of this complication requires that patients suspected to be at high risk should be screened at least once a year at an 8 AM plasma cortisol level: <83 nmol/L (3μg/dL) indicative of ACTHD and >413 nmol/L (15 μg/dL) exclusive of an ACTHD diagnosis [33]. Patients with levels of 83–413 nmol/L should ideally undergo confirmatory dynamic testing, such as insulin tolerance tests [33], in which insulin is injected at 0.05-0.15 U/kg I.V. and cortisol and glucose in blood samples are taken at 0, 30, 60, and 120 min. Glucose should be reduced by 40 mg/dL (2.2 mmol/L) and normal peak cortisol 500–550 nmol/L (18.1–20 g/dL). ACTHD treatment is mainly oral hydrocortisone, and teaches patients how to gradually increase the dose and use emergency injections ("pressure administration"), and regularly check adrenal function. Patients should carry documentation (cards, bracelets, etc.) at all times to inform emergency personnel or to screen for primary hypothyroidism and ACTHD, and treat ACTHD before a thyroid attack.

Hyperprolactinemia

Radiation-induced hyperprolactinemia is usually seen after high-dose irradiation. Hypothalamic injury can lead to a reduction in the inhibitory neurotransmitter, dopamine [65]. Hyperprolactinemia is most commonly encountered in adult women exposed to radiation doses in excess of 40Gy. In these patients, 20 to 50% of prolactin levels are mildly to moderately elevated, while prolactin levels in children and adults receiving low radiation doses are less than 5%. Radiation-induced hyperprolactinemia is subclinical in most patients. Over time, elevated prolactin levels may gradually decrease and may be normalized in some patients. This may reflect a time-dependent, slow-growing, direct radiation-induced pituitary lactotroph [76]. Radiation-induced hyperprolactinemia is not clinically significant in most patients. However, sometimes, hyperprolactinemia may be severe enough to impair the secretion of gonadotropins and cause delay or arrest puberty in children, reduced libido and impotence in adult males, and galactorrhea and/or ovarian dysfunction in adult women [75]. Symptomatic CBTS can be treated similarly to patients in the general population.

Thyroid Disorders

Radiation effects on the thyroid of thyrotoxic patients receiving RT were first reported in the 1920s. Later, radioactive iodine was used to reduce the basal metabolic rate of patients with heart disease (angina and congestive heart failure) [79]. The first report on hypothyroidism after RT for head and neck cancer was published in the 1960's [113]. It is estimated that the rate of hypothyroidism in the general population is 8-10% in women and 1-2% in men [75]. Due to the complexity of the clinical manifestations of cancer, especially in the pediatric population, abnormal thyroid function is easily overlooked in cancer patients. Under-diagnosis can have a significant impact on the treatment of hypothyroidism and malignancies. At the very least, the quality of life is adversely affected. Untreated hypothyroidism can lead to heart failure, psychosis and coma, and may reduce the effectiveness of life-saving cancer treatments, while iatrogenic causes can lead to atrial fibrillation and osteoporosis [80]. In addition to the increased risk of hypothyroidism, clinicians need to be aware that brain cancer survivors who have received thyroid radiation during childhood and adolescence also have an increased risk of developing thyroid cancer [17]. The risk of hypothyroidism increases with observation time and radiation dose to the thyroid gland, confirming previous observations. Subclinical hypothyroidism increases the risk of significant hypothyroidism and indicates the need for systematic follow-up [17].

Primary Hypothyroidism

Primary hypothyroidism is an endocrine system disorder in which the thyroid gland does not produce sufficient thyroid hormones. It can cause many symptoms such as tiredness, cold intolerance, depression, constipation and weight gain. Goiter can sometimes cause swelling in the front of the

neck [81]. Isolated subclinical hypothyroidism may show subtle clinical symptoms such as hypercholesterolemia and accelerated atherosclerosis. This hormone deficiency can slow the life-sustaining processes, damage organs and tissues throughout the body, and can lead to life-threatening complications [80]. Radiation-related primary hypothyroidism may also be caused by radiation-induced thyroid damage that does not involve immune components [82]. Levothyroxine is recommended as the first choice for treatment of hypothyroidism, because it has the efficacy to resolve the symptoms of hypothyroidism, in addition to the long-term benefits, easy administration, minimal side effects, long serum half-life, good intestinal absorption and low cost [83].

Hyperthyroidism

There are few studies on radiation-induced hyperthyroidism, and the specific incidence statistics are inadequate. Little is known about the association between hyperthyroidism and exposure to ionizing radiation. Inskip et al used individualized radiation dosimetry and a series of questionnaires to determine hyperthyroidism in order to assess the radiation doses of thyroid and pituitary gland in childhood cancer survivors associated with the occurrence of hyperthyroidism [82]. The risk of hyperthyroidism was positively related to radiation dose to the thyroid gland, but unrelated to the pituitary gland, and radiation-related risk remained elevated for >25 years. Even after adjusting the thyroid radiation dose, the increased risk of hyperthyroidism in Hodgkin's lymphoma (HL), CNS cancer, and leukemia survivors may be partly due to closer monitoring of thyroid abnormalities after radiation treatment of these cancers, especially in HL survivors [84].

Thyroid Cancer

Radiation or sporadic radiation to the thyroid gland increases the risk of thyroid tumors. Thyroid cancer is one of the most common subsequent malignancies experienced by CBTS. For survivors, thyroid exposure to direct or scattered radiation is a serious problem. Causes of radiation-induced thyroid damage include parenchymal cell damage, vascular damage, and autoimmune responses [92]. Two-thirds of the tumors induced by RT are benign, one-third are malignant, mainly well-differentiated, and rarely fatal papillary or follicular cancer [85]. These tumors appear to be clinically indistinguishable from spontaneous thyroid cancer [86]. Compared with non-radiated populations, the risk of secondary thyroid malignancies is 15 to 53 times higher in young children [68]. The dose-risk dependence is not clear; in some cases, the risk may increase to a dose of 15Gy, and then decrease with increasing doses, which may be due to cell killing [87]. Among children, females are at higher risk. Treatment with Actinomycin may further increase the carcinogenic effects of radiation [88].

How to screen for thyroid cancer in CBTS has been controversial. According to the research, false positives on ultrasound results may trigger anxiety and unnecessary extra procedures [86]. Some authors believe that the results achieved by careful clinical examination of the neck each year may outweigh the hypothetical benefits of early diagnosis obtained by ultrasound [86]. With ultrasound assessment, common abnormalities (mostly benign) without obvious nodules can be detected in patients who are irradiated [89]. Ultrasound can show structural changes and reduced thyroid volume [90]. Thyroid nodules can be detected in 40% of irradiated patients. Color flow Doppler has higher predictive value for identifying benign nodules, and vascular plaques in nodules are more likely to predict malignant tumors [85]. Although cytology may be difficult to assess due to radiation-induced atypical cells, fine-needle aspiration biopsy should be performed on palpable nodules [91]. The diagnosis and management of secondary thyroid cancer in CBTS follows the same steps as that of primary thyroid cancer in the general population [42].

Central Diabetes Insipidus

Central (neurogenic) DI occurs when antidiuretic hormone (ADH) (also called vasopressin) secreted by the posterior pituitary gland is insufficient to meet urine concentration requirements. Non-surgical patients rarely encounter DI pituitary adenomas [92]. DI can occur without anterior pituitary dysfunction. Central DI is a common complication of tumors or surgical resections involving the HP area and rarely occurs as a late-effect sequela [42, 11]. Desmopressin (DDAVP) is a long-acting analog of ADH, which mainly acts on the V2 receptor and has only minimal vasopressor activity. The lowest DDAVP dose should be used when treating DI patients to ensure adequate rest at night with minimal disturbance to individuals during the day. Due to differences in work or drug response [93], clinicians must personalize and tailor treatments to meet patient needs. Sometimes the thirst mechanism of the hypothalamus is impaired. The risk of both hypernatremia and hyponatremia is high, because patients cannot regulate water intake based on thirst [94]. A fixed dose of DDAVP and a constant dose of fluid intake are recommended along with continuous ambient temperature

and humidity conditions [95]. It is suggested that clinicians should determine whether the function of the posterior pituitary lobe is restored within weeks to months after surgery or RT. It is recommended that all diabetes insipidus patients urgently wear bracelets or necklaces to inform clinicians of their incapacitating health issues.

Osteoporosis

Because of reduced bone mineral density (BMD), CBTS patients are considered to be at high risk for osteoporosis [96]. The malignant tumor itself, malnutrition, limited weight-bearing exercise, treatment, and its sequelae can all affect BMD. The effect of cancer itself on BMD and risk of osteoporosis is unclear. The reported data on whether BMD decreases during cancer diagnosis is somewhat contradictory. Although some diseases may vary depending on the type of cancer, some diseases may alter the risk of bone metabolism and reduce bone density. Studies have shown that survivors of brain tumors are susceptible to early osteoporosis and fractures [97]. Gurney et al reported that survivors in childhood were found to be nearly 25 times more likely to report brain tumors with osteoporosis or fragile bone compared to siblings without brain tumors; 43% of these patients reported endocrine disease [98]. Furthermore, growth hormone and insulin-like growth factor I (IGF-I) are important for maintaining bone mass, as both lead to increased bone remodeling and apposition [136]. Among survivors of brain tumors in children after puberty, fracture history and untreated GHD are risk factors for reduced bone density [32]. Estrogen and testosterone also affect bone mass. Primary gonadal dysfunction is a young adult survivor of childhood cancer with known risk factors for reduced BMD [976]. Radiation targeting brain tumors and various systemic drugs appear to be directly harmful to bones. Radiation is thought to cause bone atrophy by damaging osteoblasts and blood vessels. However, Krishnamoorthy et al reported that patients who received only posterior cranial fossa radiation also reduced spine bone density throughout the body and lumbar spine [100]. Therefore, tumors themselves, or in response to treatment may release cytokines and factors that affect osteogenic and osteoclastic activities and bone modeling. Bone mineral density in survivors of CNS tumors may decrease due to treatment toxicity (glucocorticoids), growth hormone and/or sex hormone deficiency, and a sedentary lifestyle [47]. Glucocorticoids promote osteoclast activity while inhibiting osteoblast activity [101]. Malnutrition can lead to poor bone health, as this can lead to growth hormone resistance and subsequent IGF-I deficiency [102]. Poor diet can also lead to reduced dietary intake of calcium and vitamin D. Increased calcium intake leads to increased bone mass and reduced fracture risk. Some studies have shown lower serum calcium levels in CBTS, usually 25-vitamin D deficiency [101].

The dual x-ray absorptiometry (DXA) method was used to screen for BMD risk as a clinical indication for long-term follow-up [103]. The interpretation of the DXA result may be confused by delayed adolescence or short stature [106]. Plasma 25-vitamin D should be checked to help assess and treat bone loss. There are no specific CBTS management guidelines for low-BMD [42]. If BMD is still low after reaching peak quality, these survivors may be at increased risk for osteoporotic fractures later in life. Providers who care for children surviving brain tumors should assess the risk factors for low BMD in their patients, aim to maximize nutrition, exercise, vitamin D, calcium and intake, and consult an endocrinologist for possible bone health assessments and any deficiency in hormone therapy [105].

Obesity and Diabetes Mellitus

Obesity, intractable weight gain syndrome, due to damage to the hypothalamus, is a rare and devastating complication for children who survive brain tumors. The underlying mechanism of a higher risk of obesity in cancer survivors is unclear [106107]. Several risk factors have been identified to predict the development of obesity in children surviving brain tumors. Hypothalamus location, tumor histology and hypothalamus involvement, surgical range such as biopsy or gross resection (common in the hypothalamus area), and hypothalamus exposure exceeding 51Gy and the existence of hypothalamic endocrine lesions is related to the abnormal increase in BMI after treatment. Therefore, hypothalamic injury due to tumors, surgery or radiation is a major risk factor for regional development in this population [108].

In CBTS, the pathogenesis of obesity involves many risk factors, including chemotherapy, glucocorticoid therapy, cranial irradiation, and sources of psychosocial stress. Children with brain tumors, especially craniopharyngioma, also have a very high risk of developing obesity after tumor treatment [109]. As a CBTS, weight gain is often tricky and does not respond to exercise interventions and diet. This form is called "hypothalamic obesity" and is often associated with other hypothalamic endocrine diseases and is due to the hypothalamus [110]. Obesity is a catastrophic late-stage effect of cancer survivors. Obesity is a major risk factor for the general population, including diabetes, dyslipidemia, hypertension, musculoskeletal problems, sleep apnea,

impaired health, depression and social exile. These are particularly worrisome among vulnerable populations of brain tumor survivors.

Any form of hypothalamic damage (not just RT) is a risk factor for abnormally elevated BMI. The only risk factor unrelated to hypothalamic involvement is younger age at diagnosis [111]. There may also be biological causes, including persistent brain growth and myelinization until age 4 [112]. Cranial RT in younger children causes severe attention and cognitive deficits, suggesting that the developing brain is more susceptible to ionizing radiation, softening of white blood cells, with atrophy, and cavity development [113]. Cancer itself may trigger the first wave of changes in adipose tissue, which can be amplified by treatment, eventually leading to fat cell dysfunction and reduced adiponectin secretion [114]. Adiponectin directly regulates glucose and lipid metabolism and atherosclerosis and mediates endothelial function [115]. In addition, there is an inverse relationship between adiponectin and pro-inflammatory cytokines, which inhibit adiponectin synthesis [116].

The research has shown that patients with hypothalamus who are obese due to brain tumors or cranial irradiation are over-secreting insulin. The ventromedial hypothalamus (VMH) is the site of leptin, neuropeptide Y-2, ghrelin, and insulin receptors, which transduce surrounding hormone incoming signals to control the modulation of outgoing sympathetic and vagal nerves, appetite, and energy balance [117]. Hypothalamic damage (probably VMH) is evidence of major causes of obesity in brain tumor populations and downplays the role of steroids, chemotherapy, hydrocephalus and psychological factors [108]. Rose et al reported that leptin receptor gene polymorphisms may affect the obesity of all survivors in female children, especially children exposed to cranial radiation [118]. Low testosterone and estrogen levels are associated with visceral obesity, dyslipidemia, and insulin resistance, thus increasing the risk of developing metabolic syndrome [119].

Neuro-oncologists and neuro-endocrinologists use objective criteria to assess the risk of future development of obesity in this population, so close follow-up and early prevention measures can be established [94]. Obviously, if the rate of refractory weight gain has a chance to diminish, diet, exercise, and medical intervention must be undertaken early. Strategies to limit hypothalamic radiation exposure to less than 51Gy may reduce the future incidence of obesity.

Abdominal adiposity is considered an independent risk factor for the development of hyperinsulinemia (HI), impaired glucose tolerance (IGT) or diabetes mellitus (DM), and a waist-to-height ratio greater than 0.5 has the potential for clinical screening check for HI, IGT or DM [120].

Total body irradiation to hematopoietic stem cell transplantation in early childhood and the risk of developing diabetes were studied, which showed that participants with diabetes had severe insulin resistance without obesity [121, 122]. Inflammation due to tissue damage caused by radiation can interfere with insulin signaling, leading to insulin resistance. Another investigation reported that irradiation can reduce the subcutaneous mass of adipocytes, leading to major changes in the composition of adipose tissue [123]. An impaired lipid storage capacity can lead to ectopic deposition of fat in the visceral tissue, and uneven distribution of adipose tissue is associated with metabolic syndrome and insulin resistance. Other recent studies have shown that GLP-I analogs can increase insulin sensitivity and improve glycemic control in participants with lipodystrophy [124, 125].

A study in Japan reported that a young woman who survived childhood cancer had severe hypertriglyceridemia and diabetes. Her insulin sensitivity in her skeletal muscle improved after receiving metreleptin supplementation and her blood sugar was controlled without insulin [126]. For lipoprotein supplementation, lipoprotein and triglyceride profiles can be improved in some patients with lipodystrophy, possibly because high serum triglyceride levels may indicate a decrease in leptin activity, similar to general lipodystrophy. Leptin may activate residual brown adipose tissue through the central nervous system, which can promote lipoprotein lipase (LPL) activity and plasma triglyceride clearance. Unfortunately leptin activity in atrophic adipose tissue may decrease after RT [127], because total body irradiation may induce mesenchymal stem cells to differentiate into adipose tissue [128].

Metabolic Syndrome

The concept of metabolic syndrome has been around for at least 80 years. Metabolic Syndrome is also known as the insulin resistance syndrome, syndrome X and the Deadly Quartet [129]. This metabolic disorder is an all-risk factor for cardiovascular disease and was originally described by a Swedish physician, Kylin, in the 1920's as an aggregation of hyperglycemia, hypertension and gout. Later, attention was drawn to the obesity phenotype (usually associated with metabolic abnormalities associated with type 2 diabetes and

cardiovascular disease) as epidemiology (male-type obesity or android) [129]. Symptoms of metabolic disorders include glucose intolerance (impaired fasting glycaemia, impaired glucose tolerance or type 2 diabetes), insulin resistance, hypertension, dyslipidemia, hyperuricemia, central obesity, and all of which are well documented in the literature as risk factors for vascular disease.

Pediatric cancer survivors were diagnosed with type 2 diabetes, hypertension and dyslipidemia twice as many as their siblings [130], while experiencing more severe heart disease including congestive heart failure and myocardial infarction [131]. Despite a wealth of prevalence data, the underlying pathophysiological processes and mechanisms that cause the increased risk of cardiovascular disease remain unknown in pediatric cancer survivors. Cardiovascular disease may be the result of accelerated atherosclerosis caused by direct cardiovascular damage due to cancer treatment or cardiovascular risk factors associated with cancer treatment [132]. Emerging data suggest that adverse effects in childhood and poor health are related to the development of metabolic syndrome in adulthood. Fever, severe childhood illnesses and bowel infections increase the odds of obesity, hyperglycemia and dyslipidemia in adulthood [133]. The rapid rebound in weight after childhood illness is associated with insulin resistance, obesity and metabolic syndrome [134].

In addition, the risk of coronary events is more closely related to the rhythm of early-onset obesity rebound than to the actual BMI obtained [135]. Insulin resistance, diabetes and metabolic syndrome all originate in childhood. Checking for overweight and obesity every 6 to 12 months can be measured by weight, height and body mass index followed by a cardiovascular check. Survivors receiving TBI must be screened for diabetes at least every two years, whether or not they are obese or overweight [136]. Obesity management and diabetes in CBTS follow the general population. Hypothalamic treatment of obesity includes diazoxide [137], octreotide [138], and more recently glucagon-like peptide 1 receptor agonists, such as liraglutide, exenatide, dulaglutide, and leptin analogs such as metreleptin [139]. Future survival research recommendations focus on the molecular mechanisms of disease development, define new biomarkers of the disease, and detect subclinical diseases in order to screen this high-risk population, which will ultimately improve life in the rapidly growing childhood cancer cohort quality [114].

CONCLUSION

Cancer experience complicates the challenges faced by adolescents, and irreversible and progressive endocrine effects are recognized as complications of intracranial irradiation in cancer survivors [140]. Short stature may cause complex psychological problems that may affect a person's daily life, while a teenager's Tanner I/II level may cause great mental suffering. Total hypopituitarism has significant, life-threatening effects and must be diagnosed in a timely manner. Insufficient bone mass will become a burden for survivors in the future. Diabetes plus dyslipidemia will greatly lead to vascular disease and emergence of the vascular problems at a young age [141]. Sex, age, number of fractions, fraction size, total radiation therapy dose, and duration of treatment, current age, at the time of cancer diagnosis and socioeconomic status may affect the social outcomes and long-term health status of childhood cancer survivors [142,143]. Further improvements in radiation therapy technology and advances in endocrine diagnosis and treatment may better prevent and manage radiation-related injuries [63]. The endocrine function of such patients must be regularly assessed to enable timely diagnosis and enable appropriate hormone replacement therapy.

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