Endocrine late effects in paediatric cancer survivors

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Abstract

Improved survival following childhood malignancy has led to increased recognition of a multitude of late adverse effects in long term survivors, which affect their quality of life. Endocrine complications are among the commonest late effects seen and include dysfunction of the hypothalamo pituitary axis leading to impaired growth, abnormal puberty or hypopituitarism, gonadal dysfunction and infertility, thyroid gland dysfunction and neoplasms, obesity, impaired glucose homeostasis and abnormal bone development. Long term follow up is needed for early recognition and timely intervention to minimise the effects of these complications.

Introduction

The last few decades have seen a tremendous improvement in the survival of children affected by malignancy. The overall survival rate for childhood malignancy now exceeds 80% (1). However, cure has not come without a price. It is being increasingly recognised that survivors of childhood cancer go on to develop a multitude of complications during long term follow up. Among these complications, endocrine consequences are possibly the commonest encountered, affecting up to 50% of this population (2,3). Survivors of central nervous system tumours and those exposed to radiotherapy and high dose alkylating agents are especially at risk of developing endocrine related complications in later life. Endocrine late effects adversely affect the quality of life because of interference with normal growth and development and psychological adjustment. However, many of these problems can be minimised by early detection and appropriate interventions (4).

Hypothalamic-pituitary axis

Pituitary hormone deficiencies can occur in children with pituitary and suprasellar tumours, those undergoing cranial irradiation for other intracranial malignancies, those exposed to radiation therapy for orbital and naso-pharyngeal tumours and those undergoing total body irradiation as preconditioning for bone marrow transplant.

The effects of cranial irradiation depend upon age at irradiation, dose, fractionation schedule and duration after therapy. Growth hormone deficiency (GHD) is the most common and often the only hormonal deficiency observed, followed by gonadotropin, ACTH and finally TSH deficiency (2), due to differing radio sensitivity of the different hormone synthetic pathways. Lower radiation doses are associated with later onset of GHD (3).

Retardation of linear growth is a relatively common phenomenon in childhood cancer survivors. This can be caused by endocrine causes such as growth hormone deficiency and hypothyroidism, particularly in those with cranial tumours and those exposed to cranial irradiation. Other factors contributing to growth retardation include spinal irradiation and use of high doses of exogenous corticosteroids. Therefore it is recommended that the height, weight and BMI of these children are monitored every six months until growth is completed, and annually thereafter (4).

Growth hormone deficiency (GHD) following cranial irradiation usually manifests only 2 years or more after exposure. Lower doses of radiotherapy are associated with later onset of GHD. Height below the 3rd percentile or a drop of $\geq$2 percentile rankings on the growth chart or a growth velocity <4-5 cm/year during childhood are possible indicators of GHD. Assessing the bone age is important in such children, and those with a significantly delayed bone age should undergo further evaluation. However a possible pitfall may occur if a child exposed to irradiation develops both precocious puberty and GHD, where the pubertal growth spurt by sex hormones may initially mask the GHD, but compromise the final adult height even further.

In children diagnosed with GHD, GH therapy should be considered. Even though existing evidence indicates that GH therapy in these children does not increase tumour recurrence, prudence would dictate waiting for one year after completion of tumour therapy with no clinical or radiological evidence of further growth before initiating GH therapy (5). As the risk of relapse is greatest within the first 2 years from primary treatment, it is common to delay initiation of GH therapy for 2 years (6).

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The effect of growth hormone therapy on final height and change in height SDS are sub optimal in cancer survivors. Possible reasons for this include exposure to spinal irradiation, early puberty, inadequate schedules and delay in initiating therapy (2). There is an argument for combining treatment with a GnRH analog and GH to maximize growth potential in those with concurrent early onset puberty, and evidence to suggest that this is beneficial (5). However, this decision has to be individualised based on the patient's needs as well as height potential and tempo of puberty.

Puberty and, gonadal and reproductive function

Children exposed to cranial irradiation are more prone to develop central precocious puberty, presumably due to disruptive effects on the inhibitory pathways on the hypothalamus (3).While girls are more susceptible than boys at lower doses of radiation (18-24 Gy), both boys and girls are similarly prone to early onset puberty at higher doses (30-50 Gy) (6). Early puberty may be followed several years later by gonadotropin deficiency. Conversely, higher doses of radiation can cause delayed puberty due to hypogonadotrophic hypogonadism.

Gonadal dysfunction can occur in survivors of childhood cancer, due to gonadotropin deficiency or direct damage to the gonads by radiotherapy and chemotherapy. Gonadal dysfunction may manifest as delayed or arrested puberty, hypogonadism, oligospermia, azoospermia or infertility in males and as delayed/arrested puberty, primary or secondary amenorrhea, infertility or premature menopause in females.

The common chemotherapeutic agents associated with gonadal dysfunction include alkylating agents such as Busulfan, Cyclophosphamide and Ifosfamide and heavy metals such as Cisplatin and Carboplatin (7). Gonadal damage can also be caused by pelvic, abdominal, testicular, spinal or total body irradiation.

Periodic evaluation for pubertal onset and tempo, annual evaluation of Tanner staging until sexually mature and screening with baseline FSH, LH together with oestradiol in girls at age 13 and testosterone in boys at age 14 and in those with delayed puberty and features of sex hormone deficiency is recommended. In adulthood evaluation for menstrual and sexual dysfunction and infertility is necessary (7).

Preservation of fertility should be considered in patients undergoing treatment modalities with high risk of infertility. In sexually mature males, cryopreservation of spermatozoa is possible. In young sexually mature females with partners, the collection of mature oocytes for fertilization and subsequent embryo cryopreservation is an established option. Cryopreservation of oocytes is an alternative but is less successful. The options for preserving fertility in pre-pubertal children remain experimental.

Thyroid dysfunction

Primary hypothyroidism following irradiation is the commonest encountered thyroid disorder in childhood cancer survivors, and can be seen in those exposed to neck, cranio-spinal or total body irradiation (3). Although less common, hyperthyroidism and thyroid neoplasia are also associated with radiotherapy.

Children undergoing total thyroidectomy for differentiated thyroid malignancy require lifelong thyroxine replacement therapy to maintain a clinically euthyroid state with serum T4 and T3 in the near normal range, while suppressing TSH to <0.1μU/mL in most cases and to undetectable concentrations in children with extensive disease.

Body composition and glucose homeostasis

Those children with brain tumours and those receiving cranial radiotherapy are more prone to obesity and the metabolic syndrome secondary to hypothalamic damage. This propensity is also seen in those exposed to high dose prolonged corticosteroid therapy. Annual monitoring of BMI and blood pressure and two yearly measurements of fasting blood glucose and fasting lipid profile is recommended (7).

Reduced bone mineral density is recognised especially in those who received methotrexate, cyclosporine, tacrolimus, long term high dose corticosteroids and radiotherapy as well as growth hormone deficient individuals. Baseline screening with Dual energy x-ray absorptiometry is recommended for those at risk (7).

Impaired glucose tolerance is usually seen as a transient phenomenon in those receiving glucocorticoids and asparaginase, but permanent diabetes mellitus is also described following asparaginase therapy (2).

Importance of long term surveillance/follow up

The endocrine late effects of cancer therapy often evolve over time. They may cause a significant effect on quality of life of cancer survivors. These ill effects may be remediable with timely interventions. It is essential that survivors receive appropriate education and screening so that late effects can be recognized at their earliest, most treatable stage. A multidisciplinary approach is often necessary (4,8).

The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers is a useful clinical practice guideline intended to promote earlier detection of and intervention for complications that may potentially arise as a result of treatment for paediatric malignancies (7).

They are intended for use beginning 2 or more years following the completion of cancer therapy.

A well planned and coordinated long term follow up service for childhood cancer survivors involving paediatric and adult oncologists, endocrinologists, neurologists and community physicians is an increasingly felt and timely need in our country.

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