Understanding the endocrinopathies associated with the treatment of childhood cancer: part 2


Abstract
This is part 2 of an article exploring the endocrinopathies associated with cancer treatments, a growing area of care. More than 80% of all childhood cancers are treatable and the number of survivors of childhood cancer is increasing, but up to two thirds of these children reportedly present with significant health problems resulting from their treatments and about 25% of survivors have endocrine problems. This article explains how an understanding of oncology and endocrinology enables nurse specialists to educate young people about their past treatment, and its implications for their current and future health. It focuses on the specific endocrine risks to survivors of childhood cancer following treatment with chemotherapy and radiotherapy. This is the final article in a series that has illustrated the breadth of work undertaken by nurse specialists in endocrinology and oncology.

Keywords
child health, endocrinology, information needs, late effects, nurse specialists, oncology, paediatrics

Aims and intended learning outcomes
The aim of this article is to enhance the reader’s understanding of endocrinopathies associated with treatment for cancer in childhood. By completing the time out activities, you will be able to:

> Explain the effect of radiotherapy and chemotherapy on the endocrine system.
> Describe the main components of individualised care plans for young people attending late effects (LE) services.
> Discuss common endocrinopathies associated with children’s cancer treatments.

The case studies and time outs in this article refer to a fictional patient called ‘Louise’ to enable the reader to consider the effects of the absence of major pituitary hormones and the replacement therapies that may be required. While the cancer Louise has is rare, its treatments illustrate the potential effect of cancer on the endocrine system, specifically the pituitary hormones.

Radiation and the endocrine system
Radiation is an example of a treatment that can affect the endocrine system, including the pituitary gland in patients receiving radiation treatment for brain tumours or in people undergoing haematopoietic stem cell transplantation (HSCT) who receive total body irradiation (TBI). Treatments can have a negative effect on the endocrine system, although children and young people with diseases that involve the pituitary gland may have impaired pituitary function (Toogood 2004) caused by compression of a solid or cystic component of a tumour. Children who have undergone surgery before referral to specialist endocrine services may have dysfunction because of insult to the pituitary gland during neurosurgical intervention. Post-surgical pituitary dysfunction may be short-lived and require input from an endocrinologist. This input may be for only a short time or can be lifelong.

Growth hormone deficiency
Radiation is the major contributor to growth impairment (Cohen et al 1998). It can damage epiphysseal growth plates and reduce a child’s final height potential. Children and young people who require treatment of tumours in the central nervous system (CNS), orbit, face or nasopharynx, and TBI for conditioning for HSCT, will have some cranial irradiation as part of the management of their condition. Following treatment, they may require stimulation testing, which involves pharmacological stimuli to assess serum GH levels accurately. Such testing is
necessary because growth hormone (GH) is the most vulnerable hormone to radiation (Brennan et al 1998), and is prompted by failing growth identified by accurate auxology and review of growth charts.

Details about the procedure for stimulation testing can be found in the third article of this series, which focuses on clinical investigations in paediatric endocrinology (Davies and Collin 2015). Growth hormone deficiency (GHD) usually occurs in isolation from other pituitary hormones in children who have received doses of less than 30 centigray (cGy) (Darzy and Shalet 2005), where the unit gray (Gy) is a measurement of radiation dose absorbed by a patient and a centigray (cGy) is equal to one hundredth of a gray.

Presumed GHD may be more evident in some children than others, particularly on review of growth charts. The combination of a fall from previously plotted height centiles and a fall in height velocity is a good indication that formal testing may be required.

Assessment of bone age, a radiological method of assessing a growing child’s skeletal maturity, may be undertaken to compare a child’s chronological age with the age of his or her bone development. A delayed bone age may indicate there is catch-up growth to be achieved while an advanced bone age may indicate that a significant growth spurt has occurred, therefore compromising further growth and the child’s final height.

The LE experienced by people who survive childhood cancer are becoming increasingly understood. The National Institute for Health and Care Excellence (NICE) (2015), for example, supports the use of GH in survivors of childhood cancer who, following appropriate and recognised dynamic testing, demonstrate deficiency. Unlike children without clinical histories of cancer, this patient group must undergo only one dynamic stimulation test (NICE 2015).

GH is licensed for children and adults, which supports the benefits of lifelong treatment. If children are found to have GHD, they receive replacement GH therapy, although they will not usually reach their target heights.

Patients diagnosed with tumours requiring craniospinal radiotherapy, such as the aggressive brain tumour medulloblastoma, may experience disproportionate growth in which the spine becomes much shorter than the legs. Although in such cases the legs and spine respond to GH, the spine responds less because irradiation has damaged the growth plates (Ogilvy-Stuart and Shalet 1995).

Case study 1: Louise aged 5-1/2
When Louise was five years old she received chemotherapy and adjuvant radiotherapy as part of the treatment for a nasal rhabdomyosarcoma. As a result, she experiences some hormone insufficiency resulting from irradiation directed at her primary disease in the nasopharynx. After she had completed cancer treatment she attended clinic for regular follow up. Her endocrine bloods were taken in line with national protocols as surveillance.

There is a theoretical risk that GH-replacement therapy may increase the risk of relapse of the initial tumour or leukaemia and that it may play a part in the development of a secondary cancer. However, risk can be reduced if GH-replacement therapy is commenced at least 2 years after treatment has been completed (Swerdlow et al 2000).

Evidence for this risk is inconclusive and some (Ogilvy-Stuart et al 1992) caution that growth hormone therapy (GHT) may increase the risk of post-radiotherapy meningiomas. This is an example of uncertainties that survivors of childhood cancer have to manage.

When Louise was 8 she was started on GHT for faltering growth, but her height velocity remained below 0.2%. GH was not started until more than 2 years after completing treatment. Louise’s growth optimised and, when she was 12, her growth completed. Her final adult height, 155cm, was between the 0.9 and 25% percentile (Wright et al 2010). At this time Louise did not want to continue with GHT and it was discontinued.

TIME OUT 1
As case study 1 shows, and as per protocol, Louise’s GHT commenced more than 2 years after completing treatment.

» What are the psychological implications for her parents during this time?
» How would you respond to their queries about post-treatment risks?

Gonadal failure
Irradiation to the brain, and therefore the pituitary gland, can cause gonadal damage, which may lead to delayed or precocious puberty. Gonadotropin deficiency was demonstrated in 61% of a patient group who had been treated only with cranial radiation for brain tumour (Constine et al 1993).

More recently, it was reported that doses of greater than 35cGy may cause
Gonadotropin deficiency (Stava et al. 2007). The hypothalamus releases gonadotropin-releasing hormone, which stimulates the pituitary gland to release follicle-stimulating hormone and luteinising hormone, which stimulate the production of sex hormones in the ovaries and testes (Figures 2 and 3 in Urquhart and Collin 2016).

Gonadal damage may lead to absence or deficiency of sex hormones, which can prevent normal sexual development. This endocrine condition is called hypogonadotropic hypogonadism (HH). Males with HH are treated with testosterone replacement, which can be delivered in monthly or 3-monthly intramuscular (IM) injections or daily application of topical gels (Khairi et al. 2015). The injections can be administered at patients’ local GP surgeries, which reduces the amounts of time and money families would otherwise spend on travelling to specialist centres. In other patient groups, gonadal dysfunction can occur due to direct injury or irradiation to the testes and/or ovaries. Gonadal failure and infertility are related to the dose, number of exposures (expressed as fractions), time from treatment and patient age (Cohen et al. 1998).

Higher doses of irradiation are required before damage occurs to the ovaries in younger girls, but in all girls doses of greater than 20cGy to the ovaries result in complete ovarian failure. Girls who have received radiation that involves their abdomen may experience problems with future pregnancy, even radiation delivered to avoid their ovaries. An irradiated uterus can atrophy and lose elasticity, putting the mother at risk of early miscarriage and/or premature delivery (Davies and Urquhart 2007).

Abdominal, pelvic and craniospinal irradiation can also compromise gonadal function, particularly ovarian failure due to the position of the ovaries in the abdomen (Nandagopal et al. 2008). Testes are particularly sensitive even to low doses of irradiation (Davies and Urquhart 2007) and the level of testicular damage is highly dose dependent. Leydig cells, which produce testosterone, can be damaged by radiation doses as small as 2cGy, but continue to function normally.

In comparison, germ cells (sertoli), which are responsible for sperm production, can be damaged by much lower doses. This damage often results in a young male making an appropriate pubertal growth spurt and developing secondary sexual characteristics, but with reduced or absent spermatogenesis.

Precocious puberty

Precocious puberty (PP) in this patient group is well documented, but less well understood. It is defined as signs of puberty in girls younger than 8 years or boys younger than 9 years. It usually occurs following radiation doses of greater than 30cGy, although it can occur in children receiving radiation below this dose, and mainly presents in girls. PP is more frequently seen in families in which there are histories of early puberty, particularly in mothers (British Society for Paediatric Endocrinology and Diabetes (BSPED) 2011).

If puberty is allowed to advance, the epiphyses in an affected child will fuse earlier than usual. This has a significant negative effect on the child’s final height and, when PP is combined with GHD, overall growth impairment is exacerbated. Where PP and GHD occur in parallel, PP is usually treated with a GnRH analogue, which suppresses pubertal development and therefore the potential for early fusion of epiphyses, enabling a longer window of opportunity for the GH-replacement therapy to work (Davies and Urquhart 2007).

Hypothyroidism

Primary hypothyroidism, a deficiency in thyroid activity, usually occurs after radiation treatment with doses of >30cGy, although thyroid-stimulating hormone (TSH) is the most radio-resistant hormone (Davies and Urquhart 2007). Craniospinal irradiation, neck radiation and TBI are the most common treatments for childhood cancer that cause direct damage to the thyroid gland resulting in primary hypothyroidism.

Central hypothyroidism occurs when signalling mechanisms in the hypothalamic-pituitary-adrenal (HPA) axis are damaged by radiation to the head, rather than damage directly to the thyroid gland in the neck. There is a small but significant theoretical increased risk of secondary thyroid malignancy in an irritated thyroid so an elevated TSH should not be ignored (Oberfield et al. 1997). This risk appears to relate to the dose of radiation received by the thyroid gland and secondary thyroid malignancy can occur 5-26 years after treatment (Gleeson and Shalet 2001).

Thyroid nodules can also appear in survivors of Hodkin’s disease (Cohen 2005). People treated at a younger age are at greater risk of developing a thyroid cancer than those treated later. These cancers are usually well differentiated papillary or follicular carcinomas (Gleeson and Shalet 2001).
Chemotherapy and the endocrine system

Different types of drugs used in chemotherapy regimens will have different effects.

Primary gonadal failure

Primary gonadal failure is a recognised LE of toxic chemotherapeutic agents without the use of adjuvant radiation. Chemotherapeutic agents include alkylating agents, such as cyclophosphamide, ifosfamide, procarbazine, busulphan, melphalan and thiopeta; and nitrosureas, such as carmustine, lomustine, cisplatin and etoposide (Cohen 2003). The risk of infertility is highest in children who receive high dose cyclophosphamide >25g/m² although gonadal function is often preserved in children who receive lower dose cyclophosphamide <7.5g/m². Hodgkin’s disease may also have a negative influence on fertility (Rueffer et al 2001).

In females, chemotherapy alone can cause infertility and loss of sex steroid hormone production. However, pre-pubertal ovaries appear to be more resistant to cytotoxic chemotherapy agents than post-pubertal ovaries (Cohen et al 2008). Ovarian function is often retained following standard doses of chemotherapy, such as those used in treatment for acute lymphoblastic leukaemia, although premature menopause has been documented (Sklar et al 2006). Treatments involving high doses of alkylating agents, including myeloablative treatments for HSCT, are likely to result in permanent ovarian failure (Gleeson and Shalet 2001).

Premature ovarian failure (POF) has other long-term health consequences, such as the risk of reduced bone mineral density and early coronary artery disease (Schwartz 1999). Prompt detection of POF in young patients is important, therefore, to ensure timely progression through puberty. If there has been no pubertal development before treatment has commenced, the timing and tempo of oestrogen are crucial to the gradual development of secondary sexual characteristics, as well as to an appropriate pubertal growth spurt and an acceptable final height (Metzger et al 2013). Therefore, the correct timing and tempo of oestrogen is especially important in young people who have both GHD and POF who are receiving GH-replacement therapy. Once these young women have progressed fully through puberty and completed the development of their secondary sexual characteristics, their replacement therapy changes to a full replacement dose of the oral contraceptive pill or patch.

Adrenal insufficiency

Adrenal insufficiency (AI), also known as Addison’s disease, is due to adrenocorticotrophic hormone deficiency (ACTH deficiency), and is an endocrine condition defined as the inadequate production or action of glucocorticoids, principally a steroid hormone called cortisol (Moloney et al 2015). ACTH deficiency can lead to secondary adrenal failure and the risk of this increases with time following treatment with specific cancer therapies.

Children who have had cranial radiotherapy should have their cortisol levels checked once a year because of a risk of pituitary damage, which affects the control of cortisol production. Symptoms of AI are non-specific and may be missed by clinicians outside LE or endocrine services. However, for knowledgeable clinicians, symptoms such as lethargy, pallor, nausea, vomiting, weight loss for no known reason and hypotension are strong clinical indicators of AI.

One third of patients with CNS tumours have ACTH deficiency (Cohen 2003), usually as a result of tumour position and proximity to the pituitary gland or due to surgical intervention and/or radiotherapy. However, suppression of the HPA axis is uncommon in patients who have received low doses (18-24Gy) of cranial irradiation (Crowne et al 1993). AI is uncommon in children undergoing treatment for standard-risk acute lymphoblastic leukaemia (Howard and Pui 2002).

AI is often seen in patients treated with exogenous glucocorticoids, which can suppress the HPA axis and result in cortisol deficiency (Cohen 2003). This is especially the case in patients who have been receiving high dose and/or long-term steroids as part of their treatment protocols or who have received specific targeted treatments, such as HSCT, cranial irradiation and graft versus host disease. These patients’ adrenal glands are rendered atrophic, which means that appropriate supportive care, replacement therapy and emergency replacement should be addressed because untreated AI can be fatal.

Times to recovery vary from person to person depending on the degree of adrenal atrophy (Howard and Pui 2002). Where adrenal atrophy has occurred, recovery can take many months. Replacement therapy using hydrocortisone is given to mimic the activity of adrenal glands, with regular review of early morning serum cortisol levels for signs of adrenal recovery.
Case study 2: Louise aged 14
Louise is 14 years old and has regular periods. She commenced thyroxine 2 years after completing treatment. She started to experience extreme fatigue and weight loss for no known reason, and was admitted to hospital for further investigation. Early morning fasted cortisol bloods were undertaken and she was found to have delayed onset adrenal insufficiency. When her cortisol levels were checked previously they had been within the normal range. Full replacement hydrocortisone was started, which means she now carries an emergency IM injection of hydrocortisone and wears a medic alert bracelet.

Adrenal crises can occur during acute illness or stress, when the body would normally increase production of cortisol significantly (Moloney et al 2013). In these situations the replacement dose is insufficient and, if it is not increased, symptoms of hypotension and hypoglycaemia due to insufficient cortisol in the circulation may appear. These situations are life-threatening, intervention is crucial, and the young people concerned must wear medic alert bracelets. Families are trained to recognise when their children are acutely unwell, for example if episodes of diarrhoea and vomiting affect the children's ability to absorb oral replacement therapy, and in administering emergency IM injections of hydrocortisone.

Education of patients and their families is paramount to prevent adrenal crises. Guidance on adrenal insufficiency and treatment can be found in the third article in this series, which focuses on adrenal insufficiency and its management (Moloney et al 2015). A free app has also been developed to support children and parents (BSPED 2016).

TIME OUT 2
Referring to case study 2, how would you explain to Louise and her parents:
» Why thyroxine was needed and why it was given 2 years after the end of treatment?
» Why she needs cortisol?
» The circumstances in which Louise would need emergency IM hydrocortisone?
» Why she must wear a medic alert bracelet?

Care management for late effects
Endocrinopathies are now commonplace among survivors of childhood cancer. Survival rates continue to rise slowly, and LE follow up is now standardised nationally and internationally, which shows that professionals in this specialty should anticipate an increasing demand for endocrinologists to join their survivorship teams (Patterson et al 2012). Growth and development may be greater challenges for cancer survivors than for their peers. Changes in body composition are assumed to be the norm during this time, but the developmental journeys of cancer survivors with POF are manufactured and therefore different from those of their peers. These differences are emphasised by daily administration of replacement endocrine therapies, and concordance with therapy issues may arise. Early diagnosis and timely treatment of endocrine disorders can only improve overall health status for this vulnerable patient cohort (Barnes and Chemaitilly 2014).

Louise continues to be reviewed at her LE clinic. Her mother has accompanied her, but she attends the consultations alone and has specific psychosocial issues she wishes to explore with the team. Louise’s social life is busy since she started college and she is enjoying being part of a new friendship group. She expresses concerns about her appearance.

At previous follow-up clinic appointments Louise complained of enlarging breasts, feeling fat and struggling to keep up with her peers. For several years, blood tests for IGF1, the marker for GH, have shown Louise’s GH to be low, but she has been reluctant to recommence GH treatment.

TIME OUT 3
Referring to case study 3, how would you:
» Explain to Louise how GHT can help with her concerns?
» Explore Louise's anxieties about receiving a daily injection of GH for many years as a child.

Conclusion
Endocrinopathies are a well-recognised complication following treatment for cancer in childhood (Han et al 2009, Barnes and Chemaitilly 2014). Collaborative working between paediatric endocrine LE and adult...
endocrine LE teams is therefore central to effective transitions. Patient education should be specific to the individual and revisited at intervals to ensure that patients understand the risks and know who to contact to seek advice or help. As the population of childhood cancer survivors increases in number and ages, there is a greater need for knowledge sharing and education about LE among nurses in adult clinical settings and mental health nurses.

References


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TIME OUT 4

Reflective account

Now that you have completed the article you might like to write a reflective account as part of your revalidation.

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RCNi Learning modules are split into bite-sized sections and include a pre-test quiz, aims, learning outcomes, references, post-test quiz and an overall score. You can stop and start at any point during the module and pick up where you left off.
Endocrinology and childhood cancer: part 2
TEST YOUR KNOWLEDGE BY COMPLETING THIS SELF-ASSESSMENT QUESTIONNAIRE

1. Which of the following is/are most vulnerable to radiation?
   a) Thyroid stimulating hormone
   b) Growth hormone
   c) Anti-diuretic hormone
   d) Endorphins

2. Which of the following statements is untrue?
   a) Growth hormone replacement therapy (GHR) may increase the risk of leukaemia relapse
   b) GHR may play a part in a secondary cancer developing
   c) The risk increases if GHR starts 2 months after cancer treatment
   d) GHR treatment is less risky if it commences 2 years after cancer treatment ends

3. Gonadotropin deficiency is seen in what percentage of the patient group?
   a) 61
   b) 16
   c) 26
   d) 61

4. Which of the following statements is false?
   a) Abdominal, pelvic and craniospinal irradiation can compromise gonadal function
   b) Abdominal, pelvic and craniospinal irradiation can cause ovarian failure
   c) An irradiated uterus can lead to early miscarriage
   d) The testes are only sensitive to high doses of radiation

5. Testosterone is produced by the:
   a) Leydig cells
   b) Germ cells
   c) Sertoli cells
   d) None of the above

6. Precocious puberty in girls is defined as happening:
   a) After 13 years
   b) After 12 years
   c) After 11 years
   d) Before 8 years

7. Which of the following are strong indicators of adrenal insufficiency?
   a) Lethargy
   b) Weight loss
   c) Pallor
   d) All of the above

8. Adrenocorticotrophic hormone deficiency is present in what proportion of patients with central nervous system tumours?
   a) One third
   b) One half
   c) Two thirds
   d) All

9. How often do children who have had cranial radiotherapy have their cortisol levels checked?
   a) Every day
   b) Every week
   c) Every month
   d) Once a year

10. Primary hypothyroidism occurs most commonly following radiation doses of:
    a) <5 Gy
    b) <10 Gy
    c) >30 Gy
    d) <30 Gy

How to complete this assessment
This self-assessment questionnaire will help you to test your knowledge. It comprises ten multiple choice questions that are broadly linked to the previous article. There is one correct answer to each question.
* You can test your subject knowledge by attempting the questions before reading the article, and then go back over them to see if you would answer any differently.
* You might like to read the article before trying the questions. The answers will be published in the next issue.
When you have completed the questionnaire, cut out this page and add it to your professional portfolio. You can record the amount of time it has taken you to complete it.
You may want to write a reflective account. Visit journals.rcni.com/page/ns/cpd/write-a-reflective-account
Go online to do this self-assessment questionnaire and you can save it to your RCNi portfolio to help meet your revalidation requirements.
Go to rcni.com/revalidation

This self-assessment questionnaire was compiled by Anne Horner
The answers to SAQ 23 on Endocrinology and childhood cancer, which appeared in the previous issue, are:
1b, 2d, 3d, 4c, 5c, 6b (other risks are individual to each patient), 7c, 8a, 9b, 10a

This activity has taken me minutes/hours to complete. Now that I have read this article and completed this assessment, I think my knowledge is:
Excellent □ Good □ Satisfactory □ Unsatisfactory □ Poor □
As a result of this I intend to: ________________________________