Neuroendocrine Complications of Radiation and Cancer Therapy

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Contents

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Abstract

- Increased recognition is necessary for the neuroendocrine sequelae of cancer therapy, the contribution of radiation therapy (RT), and an emphasis on early detection and follow-up because of the potential impact on quality of life.
- Circulating serum growth hormone (GH) stimulates the production of insulin-like growth factor I (IGF-I) in all tissues. IGF-I mediates GH effects on growth, bone mineralization, and body composition (decreased fat deposition, increased muscle mass).
- GH deficiency is commonly believed to be the first hypothalamic–pituitary deficiency to emerge after injury to the hypothalamic–pituitary axis (HPA), followed by deficiencies of gonadotropin, ACTH, and thyroid-stimulating hormone (TSH) due to the radiation dose sensitivities; however, these deficiencies can occur in any order.
- The 5- and 10-year estimates of endocrinopathy in patients treated for base of skull tumors with proton therapy were as follows: 72 and 84 % for hyperprolactinemia, 30 and 63 % for hypothyroidism, 29 and 36 % for hypogonadism, and 19 and 28 % for hypoadrenalism.
- Rates of hypothyroidism for adults and children treated for Hodgkin's lymphoma can be as high as 65 % after radiation doses exceeding 40 Gy to the thyroid gland; lower doses are associated with a lower likelihood of injury.
- Primary ovarian failure is characterized by amenorrhoea, hypoestrogenism, and hypergonadotropism.

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- Altered GH secretion is an important and well-documented cause of poor growth in childhood cancer survivors, particularly in young children after surgery in the suprasellar region, cranial irradiation (>18 Gy), or total body irradiation (>12 Gy).
- The symptoms of central adrenal insufficiency can be subtle and include poor weight gain, anorexia, easy fatigability, and poor stamina.
- Hypothalamic damage from a tumor or cancer treatment can also result in hypothalamic obesity—unrelenting weight gain that does not respond to caloric restriction or exercise. Peak GH levels after RT decline as an exponential function of time based on mean dose of the hypothalamus.
- Routine yearly measurements of TSH and free T4 should be done in all patients who have received cranial irradiation, because the symptoms of central hypothyroidism are often subtle, and TSH secretory dysregulation after irradiation may precede other endocrine disorders.
- Any patient identified with GHD should be evaluated for possible ACTH deficiency and for central hypothyroidism.
- GnRH agonists are the most effective treatments for precocious puberty, rapid tempo puberty, or normally timed puberty that is inappropriate for height.
- Standard treatment for TSH deficiency or for primary hypothyroidism is levothyroxine replacement therapy.
- Hydrocortisone is the preferred agent for glucocorticoid replacement in children, because it is least likely to impair growth.

Abbreviations

ACTH	Adrenocorticotropin
BMD	Bone mineral density
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
GH	Growth hormone
GHRH	Growth-hormone-releasing hormone
HPA	Hypothalamic-pituitary axis
IGF-I	Insulin-like growth factor I
LH	Luteinizing hormone
OGTT	Oral glucose tolerance testing
PRL	Prolactin
QOL	Quality of life
RT	Radiation therapy
SD	Standard deviation
TRT	Testosterone replacement therapy
TSH	Thyroid-stimulating hormone
TRH	Thyrotropin (or Thyroid-stimulating hormone)-releasing hormone

1 Introduction

Neuroendocrinopathy after therapeutic irradiation represents a treatable late effect of successful cancer therapy and highlights the importance of careful follow-up for adults and children. The endocrine effects of irradiation have been extensively studied and demonstrate the systemic manifestations of late effects after localized or large volume cranial irradiation, the differential sensitivity of functional subunits of the hypothalamus and other critical endocrine organs to radiation dose, the low-dose radiation effects in normal tissues, and the benefit of newer radiation methods and modalities.

There is significant morbidity and mortality linked to the late effects of cancer therapy. Despite our understanding of the endocrine effects of cancer therapy, this information is often not considered when models of treatment outcomes and therapy effects are developed. It is possible that the contribution of endocrine deficits to morbidity and mortality is not fully appreciated. Endocrine deficiencies affect patients who do not have CNS tumors (Agha et al. 2006) as well as those whose treatment volume encompasses the hypothalamic–pituitary axis (HPA). Rare late effects of treatment most often attributed to the volume of irradiation might be linked to the indirect effects of damage to the HPA or other organs of the endocrine system. A striking example is the link between anticancer therapy for patients with pituitary tumors and craniopharyngioma. These patients are at increased risk for mortality mainly due to radiation-associated vascular disease rather than endocrinologic abnormalities (Sherlock et al. 2010). There needs to be increased recognition of neuroendocrine sequelae of cancer therapy, the contribution of radiation therapy (RT), and an emphasis on early detection and follow-up because of the potential impact on quality of life (QOL) (Stava et al. 2007). Long-term survivors are at increased risk for broad ranging side effects including metabolic syndrome, growth hormone deficiency, and cardiovascular disease (Gurney et al. 2006). The field of endocrinology primarily encompasses noncologic diseases, yet is uniquely capable of intervention to treat the late effects of cancer therapy. Endocrinologists should be consulted early in the management of patients at high risk for preexisting endocrine deficiencies and those likely to develop these common complications.

Therapeutic external irradiation to the central nervous system, head, nasopharynx, or face that includes the HPA is known to result in a variety of neuroendocrine disturbances. Although deficiency of one or more anterior pituitary hormones may ensue following radiation to the HPA, increased secretion of prolactin, and premature activation of the hypothalamic–pituitary gonadal system can also occur after

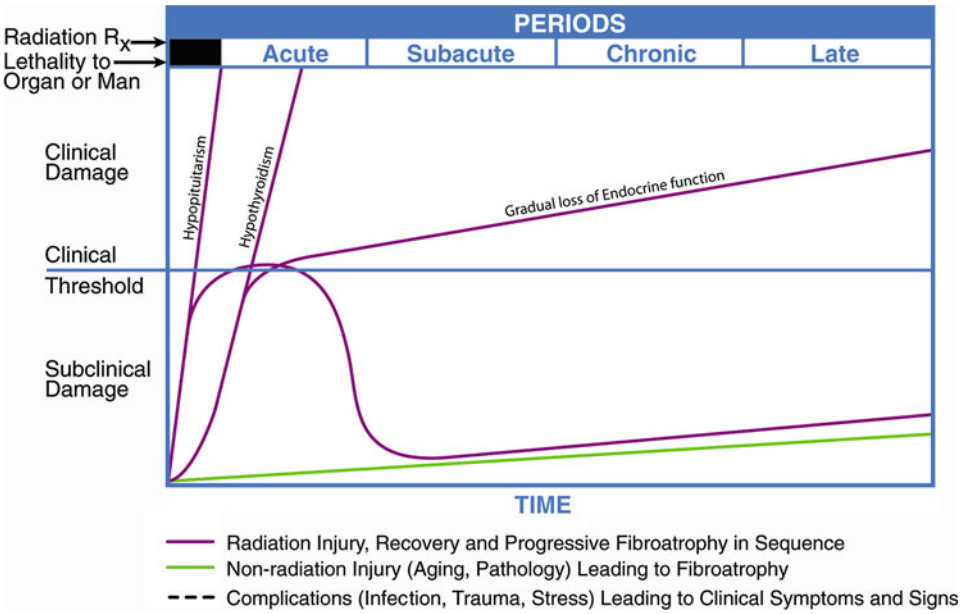

Fig. 1 Biocontinuum of adverse and late effects of the neuroendocrine system (with permission from Rubin and Casarett 1968)

treatment with radiation. In the following discussion, we have outlined the basic pathophysiology of the HPA and given a broad overview of the clinical manifestations of radiation-induced neuroendocrine dysfunction. Based on review of the current literature, we have attempted to provide dose tolerance information for each endocrine disturbance. The latter are derived from data obtained from both children and adults following irradiation of the HPA. To minimize the potential confounding effects of the primary disease and any associated surgical intervention on neuroendocrine function, we have emphasized studies in which the original lesion itself did not directly involve the HPA.

The biocontinuum of adverse and late effects are illustrated in Fig. 1.

2 Anatomy and Histology

2.1 Anatomy

The HPA is a highly complex system that allows neurological and chemical signals from the brain to be translated into endocrine responses. The hypothalamus is connected to various regions of the brain via reciprocal neuronal circuits. As a result of these afferent and efferent nerve pathways, the hypothalamus serves as a vital link between distant and diverse regions of the brain. The hypothalamus is also the site of production of several peptide hormones and biogenic amines that are the predominate regulators of the anterior pituitary hormones (Fig. 2). The vascular blood supply is unique in that the superior hypophysial artery immediately joins a complex venous plexus network which further branch into a venous capillary arborization that envelopes the pituitary gland (Fig. 2). These hypothalamic factors reach the anterior pituitary gland by way of a portal venous plexus that is composed of the primary and secondary capillary plexus. The hypothalamic regulatory factors generally stimulate the secretion of anterior pituitary hormones, but mixed stimulatory and inhibitory, as well as predominant inhibitory control, also occur. A brief summary of the regulation and mechanism(s) of action of the anterior pituitary hormones follows.

2.2 Histology

The **pituitary gland** is a small complex endocrine organ about 10 mm in length, 13 mm in width, 5 mm in height, and 0.5 g in weight. It is located in a bony fossa of the sphenoid bone, the *sella turcica*, and is covered by a dense connective tissue, **capsule**, derived from the dura mater.

Histologically, the hypophysis consists of two different tissues: adenohypophysis and neurohypophysis. The adenohypophysis (glandular portion) develops from the ectoderm at the roof of the oral cavity of the embryo. These cells migrate dorsally and form Rathke's pouch and produce a variety of hormones described below. The neurohypophysis (nervous portion) is derived from an outgrowth of the floor of the diencephalon (forebrain).

The **term anterior lobe** (Fig. 3a) refers to the pars distalis and the pars tuberalis, and the posterior lobe refers to the pars nervosa and the pars intermedia. Figure 3a is a sagittal section of the human hypophysis, clearly showing the different parts of the organ.

The pituitary is made up of different types of glandular cells (Fig. 3b).

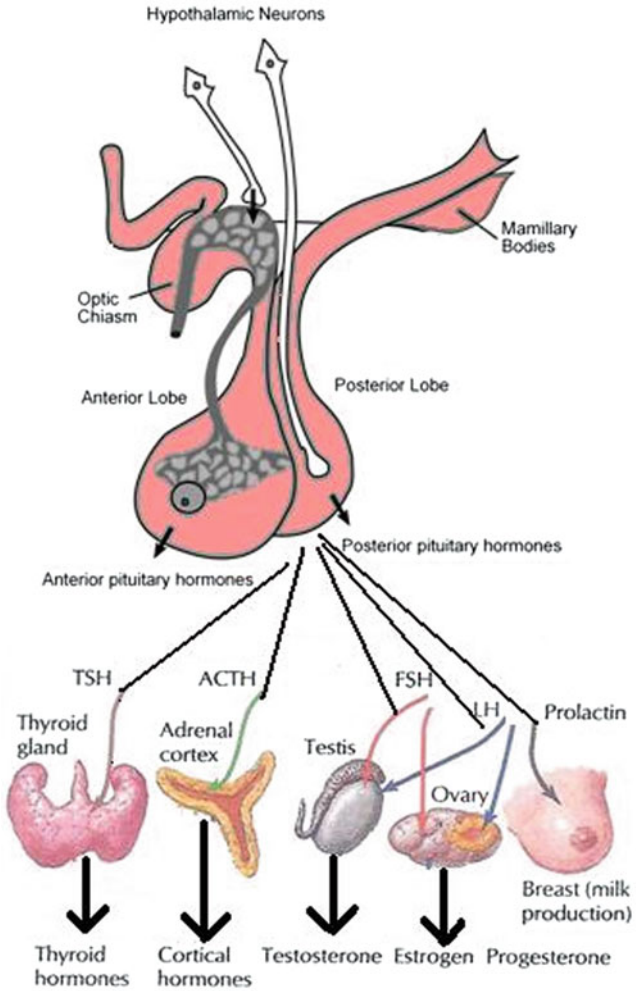

Fig. 2 Diagrammatic representation of the gross anatomy of the hypothalamic–pituitary axis and schematic representation of the anatomy of the hypothalamus and the pituitary gland, and its associated hormonal functions

The chromophils may be subdivided into two categories, acidophils and basophils.

- The acidophils, accounting for 35 % of the glandular cells in the pars distalis, are large and round or ovoid in shape. Their cytoplasm is packed with small pink or red specific granules and the secretory granules. The acidophils are composed of two cell types: somatotrophs and mammotrophs, which can be distinguished by specific immunohistochemical techniques. The somatotrophs produce growth hormone, which stimulates general body growth, particularly the growth of the epiphyses of long bones. The mammotrophs synthesize prolactin which promotes the secretion of milk during lactation.
- The basophils, representing about 15 % of the cell population of the adenohypophysis, are slightly larger in size than the acidophils. Their cytoplasm is crowded with small bluish secretory granules. Three kinds of basophils may be classified: the corticotrophs, involved in the formation of adrenocorticotropic hormone (ACTH), which promotes secretion of glucocorticoids in the cortex of the adrenal gland; the thyrotrophs, responsible for the secretion of thyrotropic hormone (thyroid-stimulating hormone, TSH), stimulating the synthesis, storage, and liberation of thyroid hormone; and the gonadotrophs, which secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Zhang 1999).

3 Physiology and Biology

3.1 Normal Hypothalamic–Pituitary Axis

The HPA is the primary interface between the nervous system and the endocrine system. The actions and interactions of the endocrine and nervous systems constitute the major regulatory mechanisms for virtually all physiologic activities. The hypothalamus has extensive neural communications with other brain regions and regulates brain functions including temperature, appetite, thirst, sexual behavior, and fear. The hypothalamus contains two types of neurosecretory cells (Fig. 2): (1) neurohypophysial neurons, which transverse the hypothalamic–pituitary stalk and release vasopressin and oxytocin from their nerve endings in the posterior pituitary, and (2) hypophysiotropic neurons, which release hormones into the portal hypophysial vessels to regulate the secretion of tropic hormones from the anterior pituitary. The six anterior pituitary hormones and their major hypothalamic regulatory factors are listed in Table 1.

3.1.1 Growth Hormone

Growth hormone (GH) is a 191-amino acid polypeptide hormone synthesized and secreted by the somatotrophs in the anterior pituitary gland in response to hypothalamic releasing hormones, primarily GH-releasing hormone (GHRH) and somatostatin. GHRH secretion is usually steady, whereas somatostatin secretion is interrupted intermittently. Somatostatin contributes to the synthesis of GH in the pituitary, but paradoxically inhibits GH release (Rose 1994). When somatostatin concentrations decrease, the tonic concentration of GHRH causes the release of GH into the systemic circulation. Ghrelin, released from the stomach during fasting, contributes to release of GH and pulses during the night (Wagner et al. 2009). Factors such as neuropeptide Y, leptin, and galanin may also regulate GH secretion. In healthy children and adults, GH secretion is pulsatile, particularly during sleep, with 2–6 pulses per night (Rose and Municchi 1999). In adolescents, additional pulses occur during the day, and the pulses have higher peaks than those seen in children and adults.

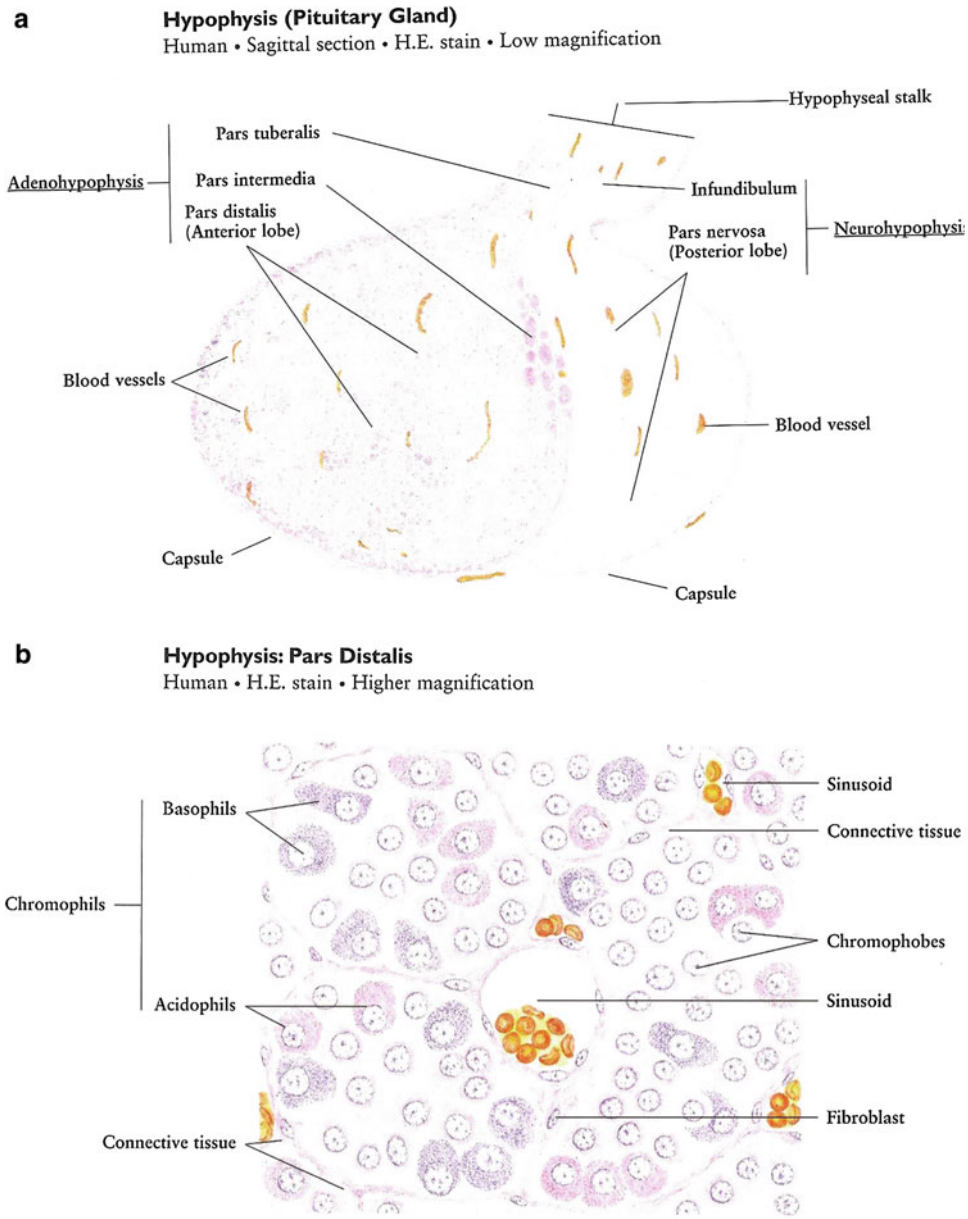

Fig. 3 Histologic examples from the **a** Anterior Lobe, **b** Glandular cells (with permission from Zhang 1999)

Circulating serum GH stimulates the production of insulin-like growth factor I (IGF-I) in all tissues. IGF-I mediates GH effects on growth, bone mineralization, and body composition (decreased fat deposition, increased muscle mass) (Vance and Mauras 1999). IGF-I is bound to IGF-binding proteins such as IGFBP3 and is transported in the blood. IGF-I and IGFBP3 concentrations are stable during the day and each reflects the integrated concentration of secreted GH.

3.1.2 Thyroid-Stimulating Hormone

Thyrotropin, also known as TSH, is a glycoprotein synthesized in the anterior pituitary. The secretion of TSH is stimulated by thyrotropin (or TSH)-releasing hormone (TRH) and inhibited by somatostatin and dopamine secreted from the hypothalamus. In persons older than 12 months of age, TSH concentration is low in the afternoon, rises dramatically (*surges*) after 1900 hours, and reaches highest concentrations between 2200 and 0400 hours (Rose and Nisula 1989). At least one-third of the trophic influence of TSH on the thyroid gland occurs at night. TRH is necessary for TSH synthesis, post-translational glycosylation, and secretion of a fully bioactive TSH molecule from the pituitary (Rose 2000). Altered TSH glycosylation, resulting in altered bioactivity, is seen in mixed hypothyroidism (central hypothyroidism with mild TSH elevation [5–15 mU/L]) (Lee et al. 1995; Rose 2001).

TSH stimulates the thyroid gland to produce thyroxine (T4) and triiodothyronine (T3). T4 and T3 circulate in the bloodstream bound to thyroxine-binding globulin and

Table 1 Anterior pituitary hormones and hypothalamic regulatory factors

Pituitary hormone	Hypothalamic factor
Growth hormone (GH)	GH-releasing hormone (GHRH)(+) Somatostatin (−)
Prolactin (PRL)	Dopamine (−)
Luteinizing Hormone (LH) and follicle-stimulating hormone (FSH)	Gonadotropin-releasing hormone (GnRH)(+)
Thyroid-stimulating hormone (TSH)	Thyrotropin-releasing hormone (TRH)(+)
Adrenocorticotropin (ACTH)	Corticotropin-releasing hormone (CRH)(+)

(+) Stimulatory, (−) Inhibitory

albumin; only small amounts are free or unbound. Free T4 undergoes intracellular deiodination to form free T3, which interacts with DNA in the cell nucleus to influence cellular mRNA and protein synthesis. Free T4 provides negative feedback at the hypothalamus and pituitary to modulate the secretion of TRH and TSH.

3.1.3 Adrenocorticotropin

Adrenocorticotropin (ACTH) is a 39-amino acid peptide hormone processed in the corticotrophs from a large precursor molecule, proopiomelanocortin. In healthy individuals, hypothalamic corticotrophin-releasing hormone and vasopressin released in two or three synchronous pulses per hour synergistically stimulate secretion of ACTH from the pituitary (Chrousos 1995). ACTH secretion is pulsatile and varies throughout the day; it peaks before the person awakens in the morning, increases with stress, and is inhibited by glucocorticoids. Because cortisol secretion is regulated by ACTH, the diurnal pattern of cortisol secretion has characteristics similar to secretion of ACTH. In addition to the negative feedback of glucocorticoids, ACTH inhibits its own secretion (short loop feedback).

3.1.4 Gonadotropins

LH and FSH are glycoproteins both stored in the same cells in the anterior pituitary. Their overall patterns of secretion vary according to the age and gender of the person. The pituitary gland produces and secretes LH and FSH in a pulsatile manner in response to a concordant episodic release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. The hypothalamic stimulus is actively inhibited between 6 months of age and the usual age of onset of puberty. This inhibition can be disturbed by tumor, surgery, or irradiation, thereby resulting in precocious puberty in children. LH stimulates testosterone production in the Leydig cells of the testes; normal spermatogenesis requires both LH and FSH. FSH stimulates follicle development in the ovary and the production of estrogen, and LH stimulates the production of progesterone from the ovarian corpus lutea after ovulation. The LH surge near the end of the follicular phase of the menstrual cycle is necessary to stimulate ovulation. Development of the ovarian follicles is largely under FSH control, and the secretion of estrogen from the follicle is dependent on both FSH and LH.

3.1.5 Prolactin

Prolactin (PRL) is a 198-amino acid polypeptide hormone synthesized and secreted from the lactotrophs of the anterior pituitary. A precursor molecule is also secreted and can constitute as much as 10–20 % of the PRL immunoreactivity in the plasma of healthy persons. The hypothalamic control of PRL secretion (primarily through dopamine release) is different than that of the other pituitary hormones in that the hypothalamus inhibits the secretion of PRL rather than stimulating it. Thus, an elevated PRL level can be a useful marker of hypothalamic disorders that leave the pituitary intact.

4 Pathophysiology

4.1 Injury of the Hypothalamic–Pituitary Axis

The HPA is vulnerable to damage by certain tumors, surgical trauma, irradiation, and chemotherapy (Constine et al. 1993; Shalet 1993). Patients with tumors in the area of the HPA (e.g., craniopharyngioma or hypothalamic and chiasmatic tumor) are at particular risk for neuroendocrinopathy (Fouladi et al. 2003; Merchant et al. 2002a, b, c, d). Many HPA injuries are attributable to damage caused by RT (see Sect. 4.2). However, the incidence of pre-RT neuroendocrinopathies in pediatric patients with brain tumors is high. Of 68 pediatric patients in one study (Merchant et al. 2002a, b, c, d), 45 (66 %) showed evidence of neuroendocrinopathy before RT, including 15 of 32 patients with tumors in the posterior fossa not adjacent to the HPA. Seventeen of the 45 patients (38 %) had abnormality in GH, 19 (43 %) in TSH, 10 (22 %) in ACTH, and 6 (13 %) in gonadotropin. In addition, patients who receive chemotherapy alone (with no history of RT or CNS tumor) may also be at risk for neuroendocrinopathy (Rose et al. 2004). Thirty-one patients were evaluated for altered growth and development in one study; of those referred patients, 48 % had GH deficiency, 52 % had central hypothyroidism, and 32 % had pubertal abnormalities (Rose et al. 2004).

GH deficiency has been commonly believed to be the first hypothalamic-pituitary deficiency to emerge after injury to the HPA, followed by deficiencies of gonadotropin, ACTH, and TSH (Shalet 1993; Spoudeas 2002); however, these deficiencies can occur in any order (Lam et al. 1991; Constine

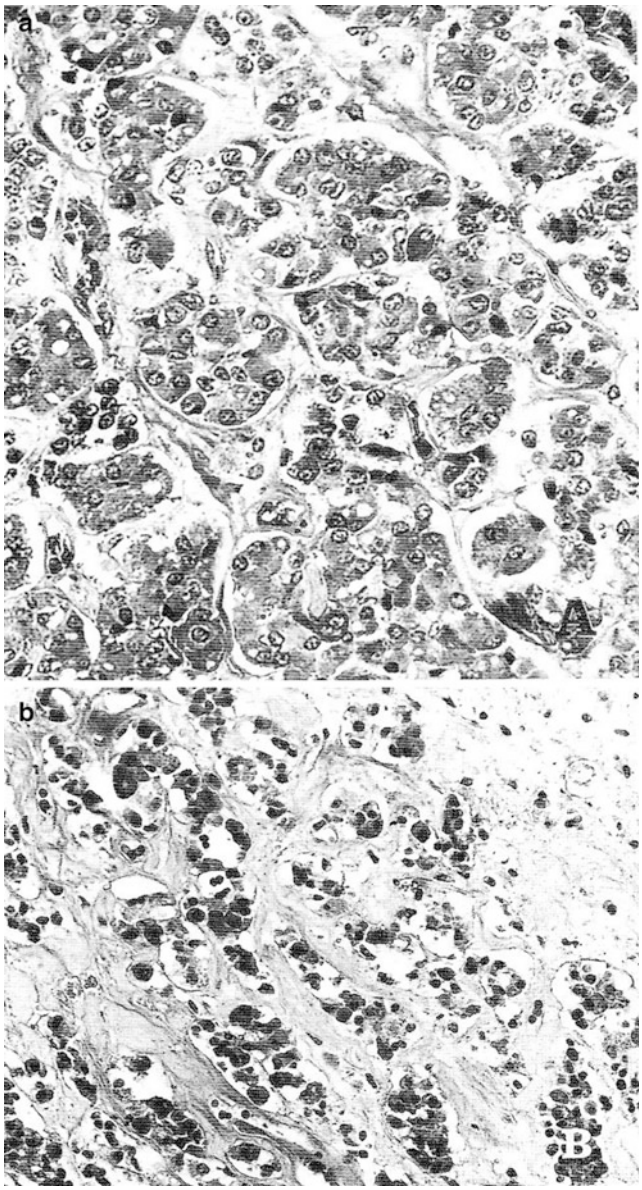

Fig. 4 Comparison of the normal epithelial cells of the anterior lobe (**a**) and the post-irradiation atrophied cells of the anterior lobe (**b**). The photomicrographs are at the same magnification. Note the severe atrophy of the epithelial cells with bands of interstitial fibrosis that also resulted from the radiation injury (with permissions from Fajardo 2001)

et al. 1993; Rose et al. 1999a, b; Merchant et al. 2002a, b, c, d; Spoudeas et al. 2003a, b). Although the most common neuroendocrinologic abnormality in survivors of childhood cancer is GH deficiency, hypothyroidism is at least as prevalent when sensitive testing methods are used (Rose et al. 1999a, b). The next most common alterations are in pubertal timing (early, rapid, precocious, delayed, or absent). ACTH deficiency, though less common than the other disorders, has more serious consequences if it is not detected. Osteopenia may result from hypothalamic–pituitary deficiency, particularly GH deficiency, hypothyroidism, and hypogonadism.

Table 2 Type and frequency of hormonal dysfunction(s) in 32 patients receiving either cranial or cranial-spinal radiation

	Cranial group	Cranial-spinal group	All
Abnormality	n = 23	n = 9	n = 32
Thyroid	17 (74 %)	5 (56 %)	22 (69 %)
Gonad[a]	11 (65 %)	3 (50 %)	14 (61 %)
Prolactin	12 (52 %)	4 (44 %)	16 (50 %)
Adrenal[b]	12 (55 %)	1 (11 %)	13 (42 %)
Number of abnormalities[a, b]			
0	1 (4 %)	2 (22 %)	3 (9 %)
1	5 (22 %)	4 (44 %)	9 (28 %)
2	7 (30 %)	1 (11 %)	8 (25 %)
3	7 (30 %)	1 (11 %)	8 (25 %)
4	3 (13 %)	1 (11 %)	4 (13 %)

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[a] Prepubertal and puberal patients ($n = 9$) excluded from gonadal category (six from cranial group, three from cranial-spinal group)

[b] One patient not tested (cranial group) three excluded from adrenal category

Hypothalamic injury resulting from tumor, surgery, or irradiation can result in unrelenting weight gain, termed hypothalamic obesity. Examples of histologic effects of RT are shown in Fig. 4.

4.2 Contribution of Radiation to Hypothalamic–Pituitary Axis Injury

RT is a significant contributor to neuroendocrine complications commonly observed after treatment for CNS tumors and tumors of the head and neck when the hypothalamus is subtended by the irradiated volume. Constine et al. reported on the radiation dose associations and frequency of HPA injury (other than GH) that occurred after treatment of CNS tumors, and demonstrated that the hypothalamus was the most sensitive component of the axis (Table 2; Constine et al. 1993). Historically, other common causes of endocrine deficiencies included CNS preventative therapy for ALL, and total body irradiation as part of preparation for bone marrow transplantation. Similar complications are observed when the HPA is incidentally irradiated in the treatment of nasopharyngeal cancer, retinoblastoma, Hodgkin lymphoma with involvement of Waldeyer's ring, and pediatric sarcomas of the head and neck (e.g., parameningeal and orbital rhabdomyosarcoma). Patients with orbital rhabdomyosarcoma are known to have excellent long-term survival; however, they are at increased risk for GH deficiency and other endocrine effects after irradiation (Forstner et al. 2006).

The timing of most hormone deficiencies after RT has been well documented (Rose 2008). Partial damage may

occur in some patients such that they respond normally to provocative tests but at much lower levels than they might have otherwise. Partial deficiencies probably have the greatest impact on children who are in their growth phase (Darzy 2009) or those with adrenal insufficiency who experience stress from intercurrent illness. The incidence and time to onset of neuroendocrine sequelae after RT are difficult to predict because of other contributors to HPA dysfunction that may coincide temporally with the administration of RT. A notable example is hydrocephalus which can cause mass effect in the region of the anterior third ventricle and generalized diminished blood flow to sensitive regions of the brain. In one study, 59 children with infratentorial ependymoma underwent provocative testing for GH, thyroid hormone, and ACTH secretion abnormality prior to RT (Lee et al. 2002). Abnormal testing was observed in 27 patients (46 %) with 30 % of the 59 manifesting an abnormality in GH secretion. Serial measurements of ventricular size from the time of diagnosis to 1 year after RT were recorded and modeled to show that ventricular size at the time of diagnosis could be used to predict pre-irradiation endocrinopathy; in addition, change in ventricular size over time could predict GH deficiency prior to irradiation. This study was remarkable because it demonstrated a relatively high rate of pre-irradiation endocrinopathy in a well-defined group and confirmed another important tumor-related cause of endocrinopathy.

Clinical data describing neuroendocrine effects of RT have been derived using generalized estimates of radiation dose under conditions where the dose to the HPA was relatively homogeneous and discrete. Examples include patients treated with single dose or fractionated TBI (8–14 Gy), cranial irradiation for ALL (18 and 24 Gy), or who have tumors of the sellar or parasellar region in which the HPA was uniformly included in the volume of prescribed dose (>50 Gy) (Fig. 5). For other diseases, the HPA may have been located within the irradiated volume for part or all of the treatment or in the gradient of dose (dose fall off) experiencing only a fraction of the daily dose administered. These circumstances make it difficult to assign a dose to the HPA and to determine the risk for late effects. These difficulties are present when the patient is seen by the endocrinologist years after treatment when retrospective dose calculations may be difficult to perform. Newer radiation techniques employ 3-dimensional imaging (CT and MR) in the planning process. The HPA and other normal tissues can be contoured on CT or MR data and the dose calculated and reported more accurately. Correlated with objective measures of endocrine effects, this information will become increasingly valuable in predicting the incidence of specific endocrine effects. Already this type of data has been modeled to predict peak GH secretion after RT (Merchant 2006) and may in the future be used to optimize RT for children.

In pediatric radiation oncology, reducing side effects of treatment is an important goal. Reducing side effects can be primarily achieved by limiting CNS irradiation only to those patients for whom the indications are clear and the benefits outweigh the risks. CNS irradiation has been effectively eliminated from the treatment of the majority of children with ALL and a significant proportion of children with low-grade glioma who may be cured with surgery. For the remainder, CNS irradiation will remain a mainstay in the treatment of most children with brain tumors. Incidental irradiation of the CNS will continue to be observed in children with ocular tumors or tumors of the head and neck destined to receive RT. Increased awareness of the importance of the hypothalamus as the effector organ in radiation-related neuroendocrine sequelae, and the use of 3-dimensional imaging in planning treatment of these tumors may lead to a reduction in late effects. Reducing the risk of complications can also be achieved by delaying the administration of RT (Shalet 1993; Spoudeas 2002; Lustig et al. 2003a, b), reducing the total dose, and by reducing the volume of irradiation. Dose reductions have been achieved for many tumors including retinoblastoma, pediatric soft-tissue sarcomas of the head and neck, and certain CNS tumors including CNS germinoma. Volume reduction has been an important area of research in the treatment of medulloblastoma, ependymoma, low-grade astrocytoma, craniopharyngioma, and CNS germinoma (Merchant et al. 2001, 2004). The risk of treating smaller volumes must be carefully balanced with objective gains documenting reductions in side effects in prospective clinical trials. To this end, the inclusion of endocrinology and its quantitative and relatively objective measures is essential. The risk of endocrine-related complications should be carefully considered in planning RT but should not be used as a reason to avoid curative therapy. Careful follow-up and evaluation will lead to early intervention and means to mitigate the consequences of irradiation.

The incidence of endocrine deficiencies and their time to onset has been well documented in children with brain tumors and patients with base of skull tumors who appear to be at risk because of the location of their tumor relative to the HPA axis, or because the radiation volume includes this structure. Thus, endocrine deficiencies are common prior to irradiation and uniformly present after irradiation in all patients with craniopharyngioma (Merchant 2006; Di Battista et al. 2006). Similarly, the incidence of hormone deficiencies is highest for children with medulloblastoma after craniospinal irradiation (Heikens et al. 1998; Laughton et al. 2008), followed by children with low-grade glioma of the diencephalon and optic pathways (Merchant et al. 2009), and less common in children with ependymoma of the posterior fossa (Spoudeas et al. 2003a, b). Complicating this picture is the occurrence of endocrine deficiencies due to incidental or scattered irradiation of non-CNS hormone-secreting tissues

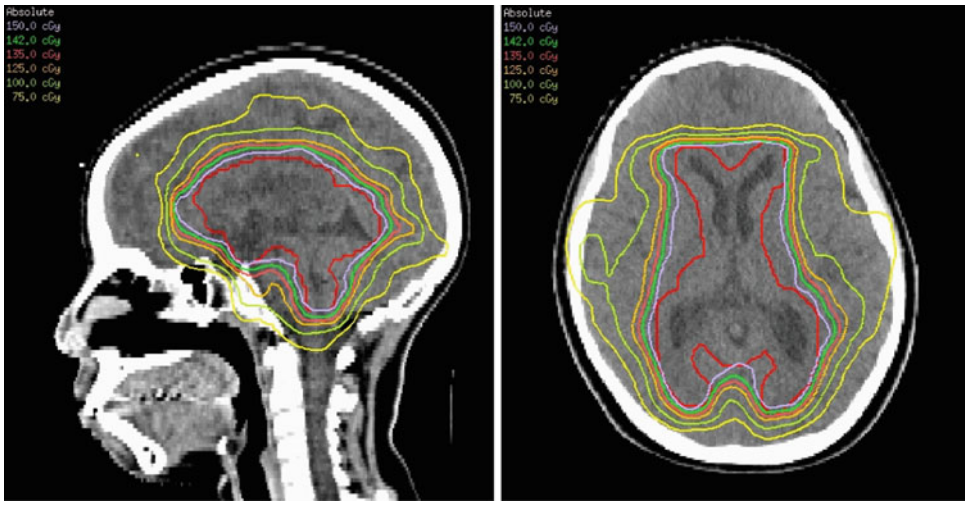

Fig. 5 Example of uniform irradiation of the HPA–whole ventricle irradiation for CNS germinoma, sagittal and axial images with overlying *isodose lines*

(Rohrer et al. 2009). For example, scattered radiation to the testes, even very low doses, results in endocrine effects for patients treated with pelvic RT (Yau et al. 2009). Nevertheless, those patients who most often develop endocrine deficiencies are those with tumors adjacent to the hypothalamus regardless of treatment modality (e.g. radiation delivery system). The 5- and 10-year estimates of endocrinopathy in patients treated for base of skull tumors with proton therapy were as follows: 72 and 84 % for hyperprolactinemia, 30 and 63 % for hypothyroidism, 29 and 36 % for hypogonadism, and 19 and 28 % for hypoadrenalism (Pai 2010). The risk of endocrinopathy was greatest among patients when the hypothalamic dose exceeded 50 Gy. These data support the work by Merchant et al. (2009) who showed that for children with low-grade glioma treated with ≥40 Gy, the 10-year cumulative incidence of hormone replacement therapy and treatment of precocious puberty were: GH 54.7 %, thyroid hormone 69.1 %, glucocorticoid 20.0 %, desmopressin 6.2 %, sex hormone 16.4 %, and GnRH agonist therapy 35.3 %. Laughton et al. (2008) showed that the incidence at 4 years of GH deficiency (93 ± 4 %), TSH deficiency (23 ± 8 %), ACTH deficiency (38 ± 6 %), and primary hypothyroidism (65 ± 7 %) was highest in patients whose hypothalamus dose exceeded 42 Gy.

4.3 Contribution of Chemotherapy to Hypothalamic–Pituitary Axis Injury

There is little doubt that chemotherapy contributes to endocrine deficiencies in long-term survivors; however, there is limited evidence because few long-term survivors in historical series reporting late effects have been cured without the use of RT. Relative exceptions include patients with leukemia, lymphoma, and extra-CNS germ cell tumors for whom chemotherapy alone was prescribed or non-TBI based conditioning regimens for stem cell transplant.

Older chemotherapy regimens used to treat HD were known to result in endocrine effects including decreased height and changes in body mass or bone mineral density (van Beek et al. 2009). Hormone deficiencies are among the leading side effects in survivors of stem cell transplantation (Leung et al. 2007). While the attribution is often given to RT, patients treated with intensive chemotherapy should be monitored for GHD (Haddy et al. 2006). Hypogonadism seems to be most common (Harris et al. 2001a, b). Alterations of gonadotropin levels and Leydig cell insufficiency persist in more than half of young patients cured from testicular cancer by cisplatin-based combination chemotherapy.

5 Clinical Syndromes

5.1 Clinical Syndromes

The LENT-SOMA provides a system for categorizing and grading the toxicity associated with hypothalamic–pituitary damage for the various hormonal axes with the exception of GH (Table 3).

5.1.1 GH Deficiency

Growth hormone deficiency is the first and most common side effect of cranial irradiation in brain tumor survivors. The risk increases with radiation dose and time after treatment. GHD is the earliest hormone deficiency and sensitive to low doses. Other hormone deficiencies require higher doses and their time to onset is much longer than for GHD (Darzy 2009). The prevalence in pooled analysis was found to be approximately 35.6 % (Mulder et al. 2009).

Altered GH secretion is an important and well-documented cause of poor growth in childhood cancer survivors, particularly in young children after surgery in the suprasellar region, cranial irradiation (≥18 Gy), or total body irradiation (≥12 Gy). Hypothalamic function is affected

Table 3 LENT-SOMA toxicity scoring for the hypothalamic-pituitary-thyroid axis

	Grade 1	Grade 2	Grade 3	Grade 4	Scoring
A. *For the hypothalamic-pituitary (thyroid axis)*					
Subjective					
Metabolic	Occasional chilliness[a]	Intermittent chilliness	Needs supplement heat		*Instructions*
Gastrointestinal	Occasional constipation[a]	Intermittent constipation	Persistent constipation		Score the 13 SOM parameters with 1–4
Weight	≥5 % gain[a]	<10 % gain	≥10 % gain		
Skin texture		Intermittent sensation of dryness	Persistent sensation of dryness		
Energy level	Occasional fatigue[a]	Intermittent fatigue	Persistent fatigue		
Objectives					
Facies		Barely noticeable puffiness and thickened lips	Obvious puffiness and thickened lips		Score = 0 if there are no toxicities
Speech quality		Barely noticeable hoarseness and slowed speech	Obvious hoarseness and slowed speech		
Skin temperature		Cool	Cold		Total the score and divide by 13
Hair texture		Difficult to comb	Brittle, splitting, hair loss		
Nodules				Palpable	
Heart rate			Slowed		
Management					
All SOM symptoms		Thyroid replacement therapy			LENT Score:
Nodules			Surgery/radionuclide therapy		
Analytic					
Basal T4	Normal limits	0–50 % decrease	>50 % decrease		Y/N Date:
Basal TSH[b]	Increased				Y/N Date:
Basal TSH[a]	Decreased				
Stimulated TSH[b]	Assessment of thyroid responsiveness				Y/N Date:
Stimulated TSH[a]	Assessment of pituitary responsiveness and hypothalamic/pituitary-thyroid axis integrity				
B. *For the hypothalamic–pituitary–adrenal axis*					
Subjective					
Activity level	Occasional fatigue	Intermittent fatigue and drowsiness	Drowsiness and weakness	Paralysis/coma	*Instructions*

(continued)

Table 3 (continued)

	Grade 1	Grade 2	Grade 3	Grade 4	Scoring
Appetite	Occasional anorexia	Anorexia/nausea	Persistent vomiting	Refractory vomiting	Score the 8 SOM parameters with 1–4
Skin color	Darkened scars	Darkened mucosa, palmar crease	Darkened skin		
Objective					
Strength			Muscle weakness	Paralysis	Score = 0 if there are no toxicities
Cardiovascular		BP 20 % below baseline	BP 20–50 % below baseline	BP > 50 % below baseline	
Metabolic	Occasional salt craving and muscle cramping	Intermittent salt craving and muscle cramping, light headedness	Persistent salt craving and muscle cramping, dizziness, syncope	Refractory muscle cramping, coma	Total the scores and divide by 8
Skin color	Darkened scars	Darkened mucosa, palmar creases	Darkened skin		
Management					
Hypoadrenalism	Hydrocortisone replacement				LENT Score:
Analytic					
Corticotrophin-stimulation test	Assessment of adrenal responsiveness and hypothalamic/pituitary-adrenal axis integrity				Y/N Date:
Corticotrophin-releasing hormone stimulation test	Assessment of adrenal responsiveness and hypothalamic/pituitary-adrenal axis integrity				Y/N Date:

C. *For the male hypothalamic/pituitary (gonadal)*					
Subjective					
Libido	Occasionally suppressed	Intermittently suppressed	Persistently suppressed	Refractory and excruciating	*Instructions* Score the 4 SOM parameters with 1–4
Objective					
Fertility				Impotent	Score = 0 if there are no toxicities
Libido	Occasional loss	Intermittent loss	Persistent loss		Total the score and divide by 4
Management					
Libido		Hormone replacement			LENT Score:
Analytic					
FSH/LH	Normal limits or borderline decreased	Decreased			Y/N Date:
Testosterone	Normal limits or borderline decrease	Decreased			Y/N Date:
Stimulated FSH/LH	Assessment of testes responsiveness and hypothalamic/pituitary-testes axis integrity				Y/N Date: Y/N Date:

(continued)

Table 3 (continued)

Grade 1		Grade 2	Grade 3	Grade 4	Scoring
D. *For the female hypothalamic/pituitary (gonadal)*					
Subjective					
Hot flashes	Occasional	Intermittent	Persistent		*Instructions*
Dysmenorrhea	Occasional	Intermittent	Persistent		Score the 10 SOM parameters with 1–4
Menstruation		Oligomenorrhea	Amenorrhea		
Libido	Occasionally suppressed	Intermittent suppressed	Persistent suppressed		
Objectives					
Ovulation			Anovulation in premenopausal women		Score = 0 if there are no toxicities
Involuntary infertility				Infertile	Total the score and divide by 10
Osteoporosis			Radiographic	Fracture	
Management					
Dysmenorrhea, hot flashes		Persistent hormone replacement			LENT Score:
Menstruation		Hormone replacement			
Osteoporosis		Hormone replacement, Calcium supplements			
Analytic					
FSH/LH/Estradiol	Assessment of hypothalamic/pituitary-gonadal axis integrity				Y/N Date:
Bone densitometry	Quantify bone density				Y/N Date:
Stimulated FSH/LH	Assessment of pituitary responsiveness				Y/N Date:

[a] Hypothalamic/pituitary-thyroid axis
[b] Primary thyroid

more than is pituitary function (Shalet 1993). In most patients with GHD, the deficiency occurs in the levels of hypothalamic GHRH and somatostatin, with a resulting loss of the circadian pulsatile pattern of GH secretion. The radiation effect on GH secretion is dependent on fraction size and total hypothalamic dose-volume (Merchant et al. 2002a, b, c, d). A large fraction size of radiation administered over a short period of time is more likely to cause GHD than is the same total dose administered in smaller fractions over a longer period of time. In one prospective study, all of the 21 children treated with a total dose of more than 45 Gy for optic pathway tumor experienced GHD and significant slowing of growth rate within 2 years after irradiation (Brauner et al. 1990). At doses of cranial irradiation higher than 30 Gy (e.g., for suprasellar or posterior fossa tumor), the risk for GHD may be more than 80 % by 10 years after RT (Shalet et al. 1976a, b). Cranial irradiation doses in excess of 24 Gy results in GH deficiency in as many as two-thirds of patients (Shalet 1993; Sklar 1997). In many younger children, GHD results from lower doses (>18 Gy). Doses of only 12–14 Gy of total body irradiation combined with chemotherapy and bone marrow transplantation also pose a significant risk for GHD (Leung et al. 2000a, b, 2002; Sklar 1997).

The growth rate is typically slow in children who are undergoing treatment for cancer and usually improves or shows catch up after completion of cancer therapy. Children whose growth rate does not improve or whose growth rate is less than the mean for age and sex should be evaluated for growth failure. Causes of slow growth other than GHD include hypothyroidism, radiation damage in growth centers of the long bones or the spine, chronic unresolved illness, poor nutrition, and depression. In individuals who have attained adult height, GHD is usually asymptomatic (Vance and Mauras 1999), but may be associated with easy fatigability, decreased muscle with increased fat mass, and increased risk for cardiovascular disease (Cummings and Merriam 2003; Gilchrist et al. 2002).

Patients with GHD, both children and adults, are at increased risk for additional endocrine deficiencies. Roughly 35 % of patients presenting with isolated GHD will eventually develop other endocrine deficiencies (Klose et al. 2009). Patients treated with cranial irradiation are at increased risk for a broad spectrum of metabolic changes including obesity, dyslipidemia, hypertension, and hyperuricemia. GH may be used to ameliorate metabolic problems (Pietilä et al. 2009). GH replacement in patients treated with TBI may have a positive impact (Bakker et al. 2007).

5.1.2 TSH Deficiency

Central hypothyroidism refers to thyroid hormone deficiency caused by a disorder of the pituitary, hypothalamus, or hypothalamic-pituitary portal circulation. In contrast, primary hypothyroidism refers to under-function of the thyroid gland itself. Primary hypothyroidism is the most common form of hypothyroidism in the general population and may occur in cancer survivors related to family history and additional contribution from the cancer therapy. The thyroid gland may have been injured through irradiation or autoimmune activity, but the central axis is intact. Central hypothyroidism in many survivors of childhood cancer is characterized by blunted or absent nocturnal TSH surge, suggesting the loss of normal circadian variation in TRH release (Pitukcheewanont and Rose 1997). Using sensitive testing of TRH and nocturnal TSH surge, Rose et al. (1999a, b) showed that central hypothyroidism, defined by a blunted TSH surge, low and delayed TSH peak or delayed TSH decline after TRH administration, is more common than previously suspected. Central hypothyroidism was found in as many as 65 % of the survivors of brain or nasopharyngeal tumors, 35 % of bone marrow transplant recipients, and 10–15 % of leukemia survivors (Rose 2000, 2001) (Table 3A).

In cancer survivors, mixed hypothyroidism reflects separate injuries to the thyroid gland and the hypothalamus (e.g., radiation injury to both structures). TSH values may be elevated and, in addition, the secretory dynamics of TSH are abnormal with a blunted or absent TSH surge or a delayed peak response (i.e., >45 min) to TRH (Rose et al. 1990, 1999a, b). This is in contrast to primary hypothyroidism in which the TSH surge and timing of response to TRH are normal. In a study of 208 childhood cancer survivors referred for evaluation of possible hypothyroidism or hypopituitarism, mixed hypothyroidism was present in 15 (7 %) (Rose et al. 1999a, b). All of the patients with mixed hypothyroidism had free T4 concentrations in the low-normal range; four had no elevation of basal TSH but elevated peak TSH, and seven had basal elevated TSH, but peak response to TRH in the normal range. Both the TRH test and the TSH surge test were required to make the diagnosis (Rose et al. 1999a, b). Among patients who received total body irradiation (fractionated total doses of 12–14.4 Gy) or craniospinal irradiation (fractionated total cranial doses higher than 30 Gy), 15 % had mixed hypothyroidism.

Secretory dysregulation of TSH after irradiation may precede other endocrine disorders. For example, 1 year after receiving cranial irradiation for nasopharyngeal carcinoma, 90 % of patients in one study had a delayed TSH peak response to TRH, which is suggestive of central hypothyroidism (Lam et al. 1991). Five years later, 64 % of this cohort had GH deficiency, 31 % had gonadotropin deficiency, and 27 % had ACTH deficiency. In another study, seven children with brain tumors who were studied prospectively after cranial irradiation (>30 Gy) had a blunted TSH surge before the onset of reduced GH concentrations (Spoudeas 1996). In

another cohort of patients with central hypothyroidism, 34 % had dysregulation of TSH secretion before the development of GH deficiency (Rose et al. 1999a, b).

Central hypothyroidism is difficult to diagnose because of its subtle clinical and laboratory presentation. It is particularly difficult to recognize in patients whose growth is complete, because slowed growth rate can no longer be used as a sign. Symptoms of central hypothyroidism (e.g., asthenia, edema, drowsiness, adynamia, and skin dryness) may have a gradual onset and go unrecognized until thyroid replacement therapy is initiated and the patient feels better (Ferretti et al. 1999). In addition to delayed puberty and slow growth, hypothyroidism may cause fatigue, dry skin, constipation, increased sleep requirement, and cold intolerance. Radiation dose to the hypothalamus in excess of 42 Gy was associated with an increase in the risk of developing TSH deficiency, 44 ± 19 % (dose > 42 Gy) and 11 ± 8 % (dose < 42 Gy) (Laughton et al. 2008).

5.1.3 ACTH Deficiency

ACTH deficiency is less common than other neuroendocrine deficits but should be suspected in patients who have a history of brain tumor (regardless of therapy modality), cranial irradiation, GH deficiency, or central hypothyroidism (Constine et al. 1993; Rose et al. 2005). Though uncommon, ACTH deficiency can occur in patients who have received intracranial radiation that did not exceed 24 Gy and has been reported to occur in less than 3 % of patients after chemotherapy alone (Rose et al. 2005) (Table 3B).

The symptoms of central adrenal insufficiency can be subtle and include poor weight gain, anorexia, easy fatigability, and poor stamina. In patients who have ACTH deficiency, as opposed to primary adrenal insufficiency, symptoms of salt craving, electrolyte imbalance, vitiligo, and hyperpigmentation usually are not observed. More overt manifestations of complete ACTH deficiency include weight loss and shakiness that is relieved by eating (hypoglycemia). Signs of adrenal crisis at times of medical stress include weakness, abdominal pain, hypotension, and shock.

Patients with partial ACTH deficiency may have only subtle symptoms unless they become ill. Illness can disrupt these patients' usual homeostasis and cause a more severe, prolonged, or complicated course than expected. As in complete ACTH deficiency, incomplete or unrecognized ACTH deficiency can be life-threatening during concurrent illness.

5.1.4 LH/FSH Deficiency

High doses of cranial radiation (≥30 Gy) are more likely to cause hypothalamic GnRH deficiency and, therefore, gonadotropin deficiency (or in some patients precocious onset puberty through loss of inhibition that later progresses to gonadotropin deficiency through loss of GnRH secretory cells). Lower doses of cranial radiation (18–24 Gy) are more likely to cause damage to gamma-aminobutyric acid secreting neurons alone (leading to disinhibition and premature activation of GnRH neurons) and therefore, rapid tempo of puberty or precocious puberty (Roth et al. 2001; Oberfield et al. 1996; Ogilvy-Stuart et al. 1994). In girls, the first signs of puberty are growth spurt and breast development (palpable breast buds or thelarche), followed by pubic hair growth and, after about 2 years, by menarche. In boys, the first sign of puberty is testicular enlargement (testes length > 2.5 cm), followed by penile and pubic hair growth and growth spurt. In most studies of normal children, pubertal milestones are attained at ages that are normally distributed, with a standard deviation (SD) of approximately 1 year (Tanner and Davies 1985). Children entering puberty more than 2 SDs earlier or later than average should be considered for endocrine evaluation. The average age that girls experience thelarche is 10 years, and that of menarche is 12.8 years; the average age when boys experience onset of testicular growth is 11 years (Table 3C, D).

Patients with gonadotropin deficiency may have delayed, interrupted, or absent puberty. Staging of puberty is usually performed by the criteria of Tanner (Tanner and Davies 1985). In survivors of childhood cancer, we initiate evaluation for delayed puberty in girls with no onset of breast development by 12 years of age or no menarche by 14 years of age; and in boys with no sign of testicular growth by 13 years of age. Boys treated with agents that cause infertility may have normal pubertal hormones but reduced testicular volume because of damage to the seminiferous tubules and reduced sperm production. Hypogonadism may result from undiagnosed primary hypothyroidism and may be reversible with thyroid hormone replacement.

5.1.4.1 Precocious or Rapid Tempo of Puberty

Precocious puberty is defined as the onset of secondary sexual development before age 8 years in girls and before age 9 years in boys (Boepple and Crowley 1996). Despite controversy that puberty prior to these ages may occur in normal children (Herman-Giddens et al. 1997), younger occurrence than age 8 or 9 years may be the only clue to the presence of pathology and should not be ignored (Midyett et al. 2003). Pubic hair, acne, and body odor are not usually part of the presentation of precocious puberty in children younger than 4 years. Precocious puberty occurs in childhood cancer survivors who have lost inhibition of hypothalamic GnRH release as a result of tumor presence, raised intracranial pressure, cranial surgery, or low dose cranial irradiation (18–24 Gy) (Burstein 1994; Ogilvy-Stuart et al. 1994). Female sex and younger age at the time of cancer treatment are risk factors for precocious puberty: precocious puberty occurs at a lower HPA dose in girls compared to

boys. In some children who have received cranial irradiation, puberty may start at a normal age and advance rapidly. Thus, tempo of progression as well as timing of onset must be monitored. Rapid puberty is also caused by loss of inhibition of hypothalamic GnRH secretion. Short adult height is the outcome of early onset and/or rapid tempo puberty. Early bony maturation may cause the child to lose 1 to 3 years of growth.

5.1.5 Hyperprolactinemia

Hyperprolactinemia has been described in patients who have received doses of radiation larger than 50 Gy to the hypothalamus, or surgery disrupting the integrity of the pituitary stalk. Hyperprolactinemia may result in delayed puberty. In adult women, hyperprolactinemia may cause galactorrhea, menstrual irregularities, loss of libido, hot flashes, infertility, and osteopenia; in adult men, impotence and loss of libido. Primary hypothyroidism may lead to hyperprolactinemia as a result of hyperplasia of thyrotrophs and lactotrophs, presumably due to TRH hypersecretion. The PRL response to TRH is usually exaggerated in these patients.

5.2 Detection

Signs and symptoms prompting immediate evaluation

Survivors of childhood cancer with any of the following 10 symptoms should be referred for the evaluation of neuroendocrinopathy: (1) slow growth rate or failure to show catch up growth; (2) failure to thrive; (3) obesity; (4) persistent fatigue or anorexia; (5) polydipsia and polyuria; (6) severely dry skin, or thin and brittle hair; (7) altered timing of onset of puberty (e.g., signs of puberty before age 9 years or in patients with short height, failure to enter puberty by age 12 years in girls and by age 13 years in boys); (8) abnormal tempo of puberty (e.g., rapid or interrupted progression of puberty); (9) galactorrhea; and (10) abnormal menstruation or sexual function.

Surveillance of asymptomatic patients

Asymptomatic patients who are at risk for neuroendocrinopathy (Table 4) should undergo the following routine yearly surveillance:

- Accurate measurements of height, or arm span (an alternative estimate of height) if the patient received total body or spinal irradiation or has scoliosis or kyphosis (factors that lead to reduced spinal bone growth or measurement)
- Accurate measurement of weight and assessment of body mass index
- Assessment of nutritional status, adequacy of dietary calcium and vitamin D intake
- Ascertainment of Tanner stage, testicular volume (as measured by Prader orchidometry), and interpretation of whether the pubertal status and tempo of progression are appropriate for age and height
- Measurement of the serum concentrations of free T4 and TSH.

5.2.1 GH Deficiency

GH deficiency should be considered in children who have a slow growth rate and a medical history that indicates that they are at risk for GHD (Growth Hormone Research Society 2000; Wilson et al. 2003). Bone age, as determined by radiographic analysis of the left hand and wrist, should be determined, and IGF-I and IGFBP3 should be measured in children who are growing too slowly. The combination of previous cranial or total body irradiation, slow growth rate, normal weight gain, no intercurrent illness, delayed bone maturation, and low plasma levels of IGF-I and IGFBP3 (i.e., concentrations lower than 1 SD of the mean for the child's age group) are highly suggestive of GHD. The diagnosis should be confirmed by GH stimulation testing (Rose et al. 1988). Evaluation of the nocturnal profile of GH secretion is rarely necessary to make the diagnosis, but the study may be abnormal in symptomatic children after cranial irradiation that have normal stimulated GH results (Blatt et al. 1984) (Table 4).

Recognition of GHD in adults is more difficult, because slow growth rate is not available as a marker. Recognition depends on clinical suspicion related to medical history. Diagnosis of GHD in adults requires evidence of other hypothalamic–pituitary hormone deficiencies and a low peak response to GH stimulation tests (Biller et al. 2002).

IGF-I receptor inhibition has been developed as a targeted therapy for a variety of adult and pediatric malignancies because IGF-I signaling has been shown to be involved in tumor cell growth and survival (LeRoith and Helman 2004). As IGF-IR blockade may lead to an increase in the production of IGF-I through normal feedback mechanisms, the effects of a paradoxical increase in circulating levels of IGF-I should be monitored.

The impact of GH deficiency in children with brain tumors

Neurons in the hypothalamus that produce GHRH are sensitive to the effects of tumor and treatment including surgery, radiation, and chemotherapy. GHD is a common side effect of CNS-directed therapy in oncology. The extent and impact of GHD before and after RT is largely unknown and should be viewed as an important research focus. Estimating the extent of this underreported problem may prompt research to identify means for intervention and improvement in screening guidelines for those at risk. We recently showed the extent and impact of GHD in GH replacement therapy on three distinct groups of children with localized brain tumors, ependymoma, and low-grade glioma and craniopharyngioma (Merchant et al. 2011).

Table 4 Evaluation of patients at risk for late effects: neuroendocrine (with permission from Halperin et al. 2010)

Late effects	Causative treatment			Signs and symptoms	Screening and diagnostic tests	Management and intervention
	Chemotherapy	Radiation	Surgery			
GH deficiency		>18 Gy to HP axis	Tumor in region of HP axis	Falling off of growth curve Inadequate growth velocity Inadequate pubertal growth spurt	Annual stadiometer height (q6 months at age 9–12 years) Growth curve Bone age at 9 years, then yearly until puberty is reached Insulin stimulation test and pulsatile GH analysis	GH therapy Delay puberty with GnRH agonist
Adrenocorticotropic hormone deficiency		>40 Gy to HP axis	Tumor in region of HP axis	Muscular weakness, anorexia, nausea, weight loss, dehydration hypotension, abdominal pain, increased pigmentation (skin, buccal mucosa)	Cortisol (a.m.) for baseline, PRN Insulin-hypoglycemia; metyrapone stimulation tests	Hydrocortisone
Thyrotropin-releasing hormone deficiency		>40 Gy to HP axis	Tumor in region of HP axis	Hoarseness, fatigue, weight gain, dry skin, cold intolerance, dry brittle hair, alopecia, constipation, lethargy, poor linear growth, menstrual irregularities, pubertal delay bradycardia, hypotension	Free T4, T3, TSH baseline, q1 year	Hormone replacement with thyroxine Anticipatory guidance regarding symptoms of hypothyroidism
Precocious puberty (especially girls)		>20 Gy to HP axis	Tumor in region of HP axis	Early growth spurt False catch-up Premature sexual maturation Female: breast development and public hair before 8 years and menses before 9 years Male: testicular and penile growth and pubic hair before 9.5 years	Height, growth curve q year Bone age q2 years until mature LH, FSH, estradiol or testosterone Pelvic ultrasound, GnRH stimulation testing	GnRH agonist
Male gonadotropin deficiency		>40 Gy to hypothalamic region	Tumor in region of hypothalamus	Delayed, arrested, or absent pubertal development: lack of diminished pubic and axillary hair, penile and testicular enlargement, voice change, body odor, acne	LH, testosterone q1–2 years GnRH testing	Testosterone replacement

The low-grade glioma cohort included 78 patients with a median age of 8.7 years treated between 1997 and 2006. Using standard provocative testing, pre-irradiation GHD was identified in 50 % (18/36) of children at a level less than 10 ng/ml. Based on a level of 7 ng/ml, 25 % of the children 9/36 were identified as having GHD prior to

radiation. The accessed 5 year incidence of hormone replacement therapy in patients with low-grade glioma was 57 % for thyroid hormone, 44 % for GHRH, 43 % for GNRH agonist, and 22 % for cortisol replacement. The median follow-up on these data was 54 months (Fig. 6a) (Merchant et al. 2009).

A similar assessment was performed in 88 children with ependymoma. GHD was evaluated before and after RT and the incidence of hormone replacement therapy. Considering patients treated between 1997 and 2006 with a median age of 2.8 years, pre-irradiation GHD was identified in 28 % (24/87) using a cut-off level of 10 ng/ml. The pre-irradiation incidence of GHD was 14 % (12/87) using a cut-off level of 7 ng/ml. The 5-year incidence of hormone replacement therapy was 26 % for thyroid hormone, 18 % for GH, and 6 % for control (Fig. 6b).

Patients with craniopharyngioma were markedly different. They had the highest incidence of pre- and post-irradiation GHD and hormone replacement therapy. Among 27 patients with craniopharyngioma treated between 1998 and 2003, with a median age of 7.9 years, pre-irradiation GHD was identified in 81 % (22/27) using a cut-off of 10 ng/ml. The incidence was 53 % (19/36) using a level of 3 ng/ml (severe GHD). The baseline, 6, 12, and 24 months incidence of hormone replacement therapies were 0, 0, 46 and 71 % for GH; 43, 46, 54, and 57 % for desmopressin; 75, 79, 89, and 93 % for thyroid hormone; and 71, 75, 75, and 75 % for adrenal hormone replacement.

GH secretion has shown the highest level of sensitivity to the effects of RT on hypothalamus. Peak GH levels after RT decline as an exponential function of time based on mean dose of the hypothalamus. These data are consistent among patients with ependymoma, low-grade glioma/optic pathway glioma, and craniopharyngioma. The marked difference is that children with craniopharyngioma often have a very high rate of pre-irradiation endocrinopathy and a fall to near undetectable GH levels only 12 months after RT. Likewise, patients with low-grade glioma or optic pathway glioma tend to have a high incidence of pre-irradiation endocrinopathy and GHD. Their mean GH level prior to RT, excluding patients who have definite pre-irradiation deficits, tends to be higher than in those CNS patients with craniopharyngioma, yet lower than the ependymoma group. However, patients with ependymoma are more susceptible to the effects of hydrocephalus. Patients with optic pathway tumors and craniopharyngioma (suprasellar location) tend to have a higher incidence of pre-irradiation endocrinopathy based on tumor and surgical factors.

We have shown in children with ependymoma that pre-irradiation GHD affects baseline and longitudinal change in cognitive function. The baseline effects are most prominent for IQ, memory, and measures of academic achievement including mathematics scores (Fig. 6c). The effect of pre-irradiation GHD on longitudinal clinical changes after RT is most notable for reading scores (as a part of academic achievement testing). Similar findings have been noted evaluating cognition after RT in patients with optic pathway glioma. GHD is shown to impact reading scores over time (Fig. 6d). Though the changes over time were statistically significant compared to no change, they were not statistically different in the group that did not have GHD. The impact was most notable for reading scores in IQ. Finally, among children with craniopharyngioma, pre-irradiation GHD impacted both baseline and longitudinal change in IQ and reading scores (Fig. 6e). The assessment of pre- and post- irradiation GH secretion abnormalities in children with brain tumors can be divided into whether patients had hydrocephalus, HPA tumor invasion, or extension to adjacent regions. Treatment-related GHD most often resulted from surgical intervention with direct damage to the hypothalamus, but also the insidious effects of RT and or chemotherapy.

Pre-irradiation GHD can predict post-irradiation effects on cognition, along with endocrine effects and other somatic effects not discussed here. Post-irradiation GHD is known to correlate with hypothalamic dose. Post-irradiation GHD can predict functional outcomes. Patients at risk for GHD include those with brain tumors, head and neck tumors (including nasopharyngeal cancer), and retinoblastoma. Brain tumor patients included those with medulloblastoma, ependymoma, craniopharyngioma, and low-grade glioma (most often central or optic pathway tumors). GH testing regimen included stimulation using arginine and carbidopa-levodopa. This testing was performed in our prospective institutional series at baseline, 6 and 12 months after RT. In previous studies, we also tested at 36 and 60 months. The value of testing after 3 years was limited, since within 3 years the majority of children who will require GH replacement therapy were receiving that treatment thus skewing the data for the 60 month evaluation. Requirements include the test agents and IV placement, thus, requiring a dedicated nursing support team. Having detailed hypothalamic dosimetry from conformal treatment techniques adds to the value of this testing.

5.2.2 TSH Deficiency

We suggest that routine yearly measurements of TSH and free T4 be done in all patients who have received cranial irradiation, because the symptoms of central hypothyroidism are often subtle, and TSH secretory dysregulation after irradiation may precede other endocrine disorders (Lam et al. 1991; Rose et al. 1999a, b). The diagnosis of hypothyroidism may be delayed in as many as one-third of patients, if TSH secretion is not tested until GH deficiency becomes apparent. Such a delay may be acceptable in a minimally symptomatic adults. In children, however, the

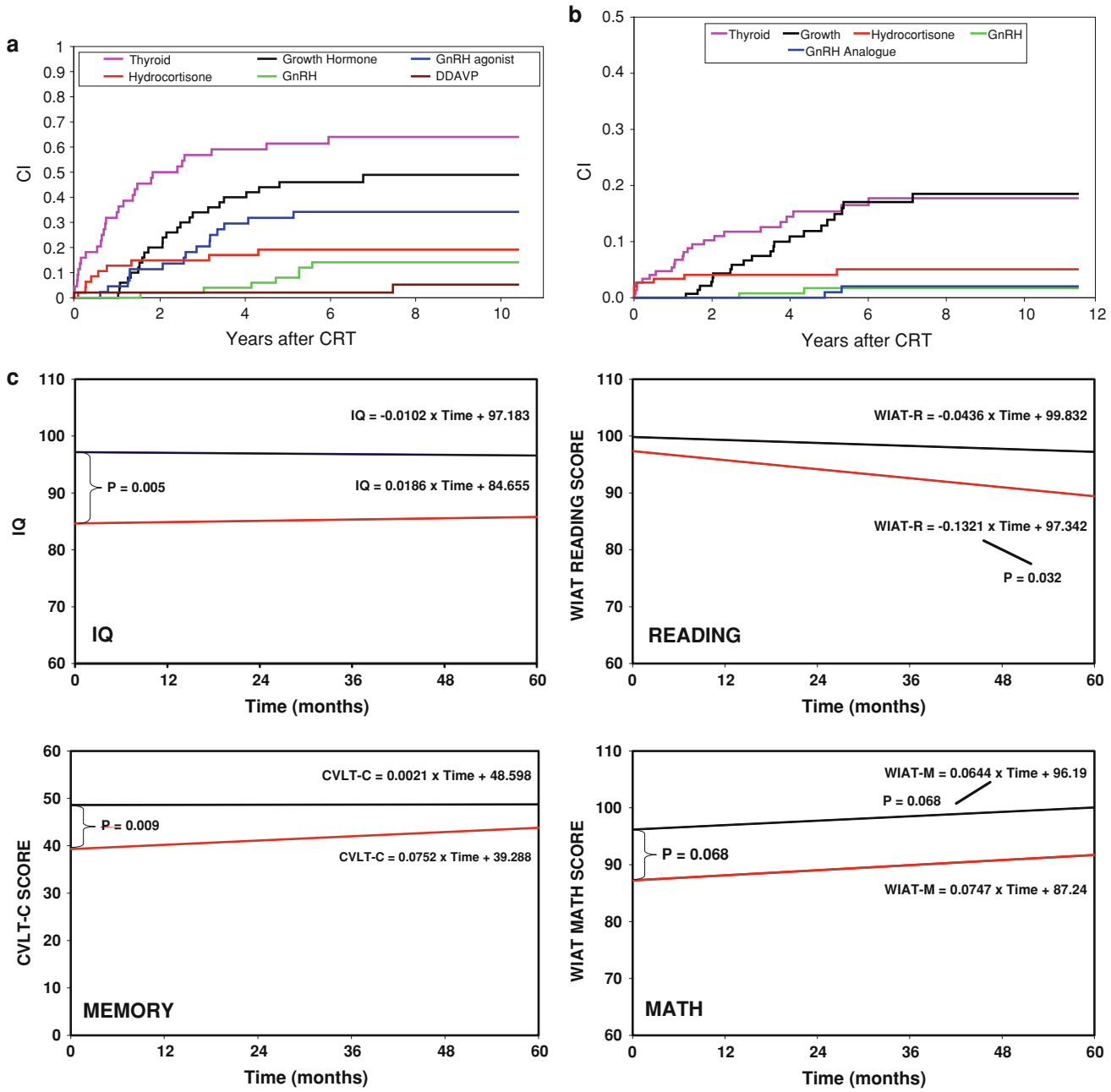

Fig. 6 **a** Incidence of hormone replacement therapy following RT for an optic pathway glioma. **b** Incidence of hormone replacement therapy following RT for a posterior fossa ependymoma. **c** The impact of growth hormone deficiency on IQ, memory and measures of academic achievement including mathematics scores, both at baseline (far *left-hand side* of the graphs) and over time in patients with ependymoma. *Red lines* are patients *with* growth hormone deficiency pre-therapy, compared to those without (*black line*). **d** The impact of growth hormone deficiency on IQ and reading scores both at baseline (far *left-hand side* of the graphs) and over time in patients with optic pathway glioma. *Red lines* are patients with growth hormone deficiency pre-therapy, compared to those without (*black line*). **e** The impact of growth hormone deficiency on IQ and reading scores both at baseline (far *left-hand side* of the graphs) and over time in patients with craniopharyngioma. *Red lines* are patients with growth hormone deficiency pre-therapy, compared to those without (*black line*). *GHD* growth hormone deficiency

potential functional implications of hypothyroidism and lost growth opportunity require early intervention (Rose 1995). Early diagnosis of mild hypothyroidism permits early intervention to improve growth velocity and QOL (Table 3A).

Free T4 and serum TSH are the best screening tests for thyroid status. Free T4 below the normal range without TSH elevation is strongly suggestive of central hypothyroidism. However, many patients with central hypothyroidism have free T4 concentrations in the lowest third of the normal

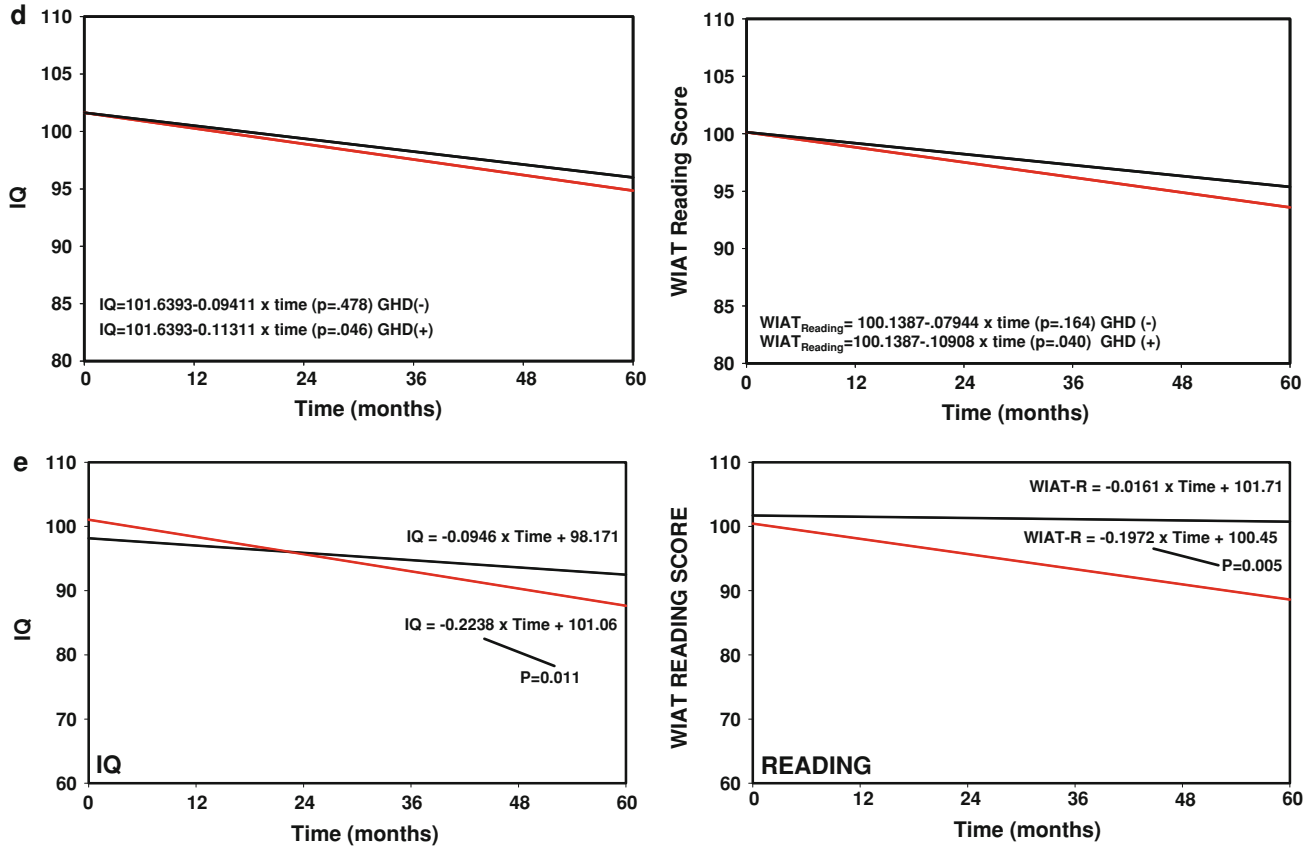

Fig. 6 (continued)

range (Rose 1995, 1996; Rose et al. 1999a, b). The first laboratory evidence of central hypothyroidism may be a small decline in free T4. In a person not on pharmacologic steroids, obtaining a TSH at 8 a.m. and one at 4 p.m. can be informative: an 8 a.m./4 p.m. TSH ratio $\leq$1.3 confirms central hypothyroidism (Rose 2010). If further testing confirms central hypothyroidism, treatment should be initiated even though free T4 is still within the normal range because it is likely to be below the individual's optimal set-point. Both the TRH test and the TSH surge test were performed in our patients when the free T4 was in the lowest third of the normal range and TSH was not elevated. The TRH test confirmed 60 % of cases of central hypothyroidism after cranial irradiation. Measurement of the nocturnal TSH surge confirmed 71 % of cases. Measurement of both the TSH surge and the response to TRH were considered optimal in order to identify all cases (Rose et al. 1999a, b); unfortunately TRH is no longer available in the United States as a test agent.

5.2.3 ACTH Deficiency

For patients at risk for ACTH deficiency (e.g., those who received $\geq$30 Gy irradiation to HPA), surveillance should include the yearly measurement of plasma cortisol concentration at 0800 hours. If cortisol level is below 18 μg/dL (497 nmol/L) at 0800 hours, then further evaluation should be directed by an endocrinologist. The optimal evaluation for ACTH deficiency is controversial (Rose et al. 1999a, b, Kazlauskaite et al. 2008). Measurement of the basal plasma ACTH concentration usually can distinguish primary adrenal disease from central adrenal insufficiency if the ACTH assay is reliable, and there is no urgency in establishing the cause of adrenal insufficiency. Patients with primary adrenal insufficiency have a high concentration of plasma ACTH at 0800 hours; ACTH levels can be as high or higher than 4000 pg/mL (880 pmol/L). In contrast, plasma ACTH concentrations are low or low-normal in patients with secondary or tertiary adrenal insufficiency. The normal value at 0800 hours is usually 20–80 pg/mL (4.5–18 pmol/L) (Table 3B).

The approach is somewhat different in patients who present in hypotensive crisis. These patients may have adrenal insufficiency or another cause of hypotension. Furthermore, adrenal insufficiency, if present, may have been caused by infection, hemorrhagic diathesis, or metastatic disease that requires prompt diagnosis and treatment. In these patients, measurement of basal serum cortisol followed by the low-dose ACTH stimulation test (see below)

provides the most rapid and reliable diagnosis. A basal plasma ACTH measurement can be ordered at the same time, but diagnosis and treatment must proceed immediately without waiting for the ACTH and cortisol results.

The gold standard for diagnosis of ACTH deficiency is failure of serum cortisol to rise above 20 μg/dL (552 nmol/L) in response to insulin-induced or spontaneous hypoglycemia (Kazlauskaite et al. 2008). Another method of diagnosis involves the administration of metyrapone to block the adrenal conversion of 11-deoxycortisol to cortisol. This method stimulates the production of ACTH and a secondary increase of 11-deoxycortisol. Failure of the concentration of 11-deoxycortisol to rise above 7 μg/dL (200 nmol/L) in the presence of a low serum cortisol (below 5 μg/dL [138 nmol/L]) signifies ACTH deficiency (Clayton 1996; Shankar et al. 1997).

An attempt to simplify the evaluation of the hypothalamic-pituitary-adrenal axis led to development of the 1-h ACTH test (or high-dose ACTH test), which consists of the administration of ACTH (250 μg/m^2) by intravenous infusion over 1 min (Rose et al. 1999a, b). Serum cortisol is measured 1 h later and is normally greater than 20 μg/dL (552 nmol/L). Patients with complete ACTH deficiency (in whom the adrenal glands have not been exposed to ACTH for 4–10 weeks) fail to respond with a 1-h serum cortisol concentration more than 20 μg/dL (552 nmol/L) (Soule et al. 1996). In contrast, patients with partial ACTH deficiency or recent onset of complete ACTH deficiency may have a normal serum cortisol response to this dose of ACTH, and ACTH deficiency may not be detected by this test.

The low-dose ACTH test is the most sensitive test for partial ACTH deficiency. A meta-analysis performed by Kazlauskaite et al. (2008) suggested that the low-dose ACTH test (1 mcg/m^2, up to 1 mcg) is more sensitive for the diagnosis of partial ACTH deficiency than the 250 mcg ACTH test. In this test, a more physiologic dose of ACTH (1 μg/m^2) is administered by intravenous infusion over 1 min, and blood for a serum cortisol assay is drawn 20 min after the infusion. Peak serum cortisol higher than 20 μg/dL (552 nmol/L) is considered normal, and peak serum cortisol lower than 18 μg/dL (497 nmol/L) is considered low. Patients with cortisol peaks between these values have indeterminate results; these patients should be treated with glucocorticoids when they are ill and will require further evaluation (Soule et al. 1996). Further evaluation can include a second low-dose ACTH test or metyrapone administration 2 months to 1 year later.

The low-dose and high-dose ACTH stimulation tests have supplanted insulin-induced hypoglycemia and metyrapone in clinical practice. The results are similar to those obtained with insulin-induced hypoglycemia; in addition, ACTH tests can be performed without a physician being present and are less expensive.

5.2.4 LH/FSH (Gonadotropin) Deficiency

During the range of ages in which puberty is normally expected to occur, breast development, pubic hair growth and distribution, and vaginal estrogenization should be monitored every 6 months in those girls at risk of having LH/FSH deficiency. Similarly, testes size, pubic hair growth and distribution, and phallus length should be monitored every 6 months in boys. Testicular size in some boys may be small for their virilization because of radiation or chemotherapy-induced damage to the seminiferous tubules (Table 3C, D).

Measurement of bone age, serum LH, FSH, and sex steroid (testosterone or estradiol) should be performed in children with delayed or interrupted progression of puberty. Evaluation by an endocrinologist should be prompted by the absence of progression of puberty by 1 year after completion of cancer therapy in girls >13 years of age, or in boys >14 years of age. Stimulation testing with synthetic GnRH provides more information than does a single, randomly drawn level of LH and FSH. An alternative to a GnRH stimulation test may be a serum sample for LH, FSH, and testosterone or estradiol drawn between 4 and 8 a.m., at the time shortly after nighttime pulses of LH have been occurring.

5.2.4.1 Precocious Puberty

Precocious puberty is diagnosed if the onset of secondary sexual development is before age 8 years in girls and before age 9 years in boys. A radiograph of the left hand and wrist may show a bone age that is advanced compared to chronologic age. However, bone age may be consistent with chronologic age or even delayed in a child who has concurrent GH deficiency or hypothyroidism, and who has not undergone a growth spurt. Because concurrent GH deficiency may not be discovered until after successful treatment of precocious puberty, we routinely perform provocative GH testing in patients with precocious puberty who have a history of cancer.

5.2.5 Hyperprolactinemia

Hyperprolactinemia is diagnosed when the serum level of PRL is elevated. The PRL level should be periodically measured in patients with symptoms outlined above (Sect. 3.6) and in those who received more than 50 Gy of irradiation to the hypothalamus. The definitive PRL level should not be drawn in the hour or two after breast examination or nipple stimulation.

6 Radiation Tolerance

6.1 GH Deficiency

GHD is the most common and frequently the only anterior pituitary deficit to develop after cranial irradiation. It has

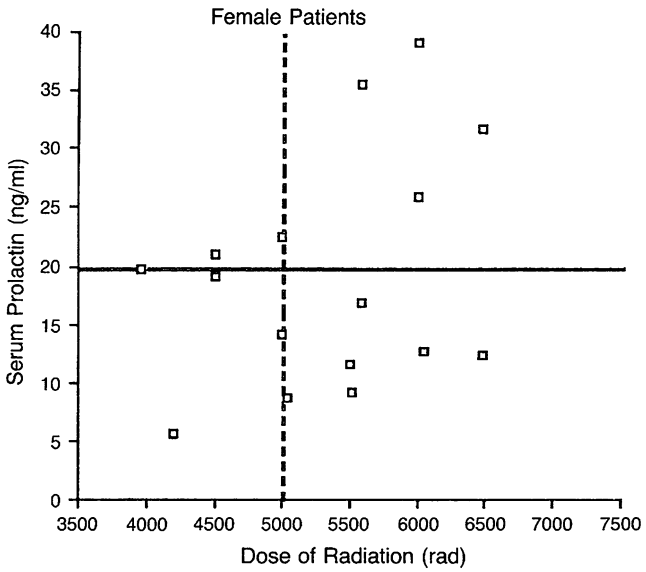

Fig. 7 Relationship between the serum prolactin concentration to the estimated dose of radiation to the HPA in females with brain tumors. Note increased levels of prolactin with higher RT doses (reprinted by permission of The New England Journal of Medicine, Massachusetts Medical Society, Constine et al. 1993)

been noted following conventional fractionated radiation with doses ≥18 Gy to the HPA and following total doses as low as 9–10 Gy when given in a single dose (e.g., total body irradiation for BMT). Current data suggest that nearly all children treated with doses in excess of 35 Gy will develop GHD, which generally occurs within the first 5 years after treatment. In children, a spectrum of GH neurosecretory dysfunction exists that appears to be dose dependent. When the HPA dose is >30 Gy, reduced GH following both pharmacological testing as well as physiological studies is noted. Following 20–40 Gy, spontaneous GH secretion remains low, while the GH response to provocative agents is often normal. The threshold dose for GHD appears to be higher in adults, and for any given dose of irradiation the incidence of GHD is lower in adults than in children (Constine et al. 1993) (Figure 7).

6.2 TSH Deficiency

The data, again, are limited and the threshold dose required to induce TSH deficiency is not known. At doses to the HPA under 40 Gy, TSH deficiency is very unusual. In two pediatric series following HPA irradiation of 40–50 Gy, the incidence of TSH deficiency was 3–6 % after a mean follow-up of 9–10 years. The incidence of TSH deficiency increases substantially, when the HPA dose exceeds 50 Gy. Although some studies have suggested that TSH is the anterior pituitary hormone least likely to be affected by irradiation, Constine et al. noted a 65 % incidence of TSH deficiency in their patients treated with a mean dose of 57 Gy (Constine et al. 1993).

6.3 ACTH Deficiency

The data concerning the relationship between HPA irradiation and the evolution of ACTH insufficiency are quite limited. Moreover, interpretation of the data are complicated by the fact that different investigators use different methods of assessment and the incidence of adrenal insufficiency tends to vary, depending on the testing procedure employed. Clinically apparent ACTH deficiency is distinctly uncommon in patients receiving HPA irradiation <50 Gy. Following doses >50 Gy, the reported incidence of ACTH deficiency varies from 18 to 35 % during follow-up periods ranging from 5 to >15 years. Limited data suggest that the incidence of ACTH deficiency may be higher in older patients compared to children and adolescents.

6.4 Gonadotropin Deficiency

Detailed information on the threshold dose for LH/FSH deficiency are lacking. Nonetheless, it appears to be quite rare following HPA doses <40 Gy. There is a progressive increase in incidence as the dose to the HPA exceeds 50 Gy. At the higher dose range, gonadotropin deficiency has been noted in 20–50 % of patients followed long term, making it the second most common pituitary abnormality in many series.

6.4.1 Early Sexual Maturation

This phenomenon, originally described in patients treated with relatively high-dose cranial irradiation (24–45 Gy), is probably most often noted following 18–24 Gy as is given for CNS prophylaxis for leukemia. It is likely that at doses greater than 50 Gy, the prevalence of early puberty decreases as the incidence of gonadotropin deficiency increases.

6.5 Prolactin (Hyperprolactinemia)

Elevated plasma concentrations of prolactin are seen infrequently in patients treated with HPA irradiation under 40–45 Gy. Mild increases in prolactin are particularly commonly observed after cranial radiotherapy with doses greater than 50 Gy, especially among women (Fig. 7) (Constine et al. 1993). The overall incidence of hyperprolactinemia has varied from 20 to 50 %.

7 Chemotherapy

At the present time, there is very little data to support the contention that chemotherapeutic agents, either singly or in combination, have the capacity to permanently impair anterior pituitary function. Although certain drugs (e.g., cyclophosphamide, vinca alkaloids, cisplatin) have been associated with transient episodes of inappropriate vasopressin secretion, chronic abnormalities of posterior pituitary function have not been reported following treatment with radiation or chemotherapy. For example, Fig. 8 illustrates data reporting the impact of chemotherapy with or without RT on height in survivors of acute lymphoblastic leukemia, suggesting that RT has a far greater impact on growth than does chemotherapy.

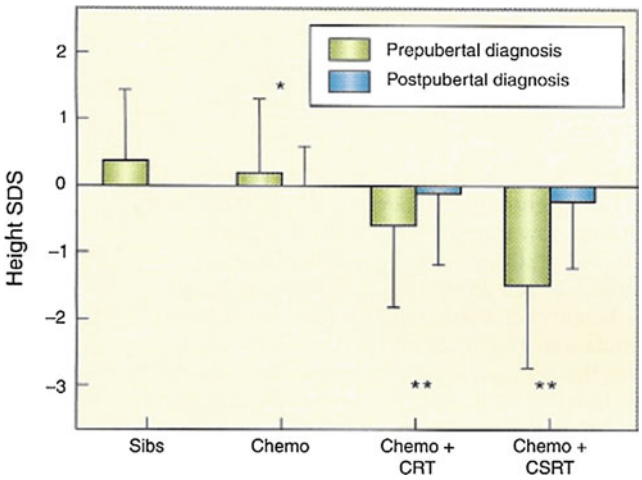

Fig. 8 Height standard deviation scores (SDS) for ALL survivors treated pre- or post-pubertally with chemotherapy alone, cranial or craniospinal RT (with permission from Chow et al. 2007)

8 Special Topics

8.1 Diabetes Insipidus

Urine specific gravity of patients with diabetes insipidus is usually lower than 1.010 (<300 mOsm/L), unless the patient is severely dehydrated. In most of these patients, serum osmolarity is slightly increased, and the plasma concentration of antidiuretic hormone is inappropriately low for the osmolarity. However, patients with an intact thirst mechanism may be able to drink sufficiently to avoid laboratory abnormality. Symptoms of polydipsia, polyuria, and nocturia or enuresis may be the only evidence of diabetes insipidus. In partial diabetes insipidus, a water deprivation test may be needed to establish the diagnosis and to rule out other causes of polyuria.

Diabetes insipidus may be caused by histiocytosis, germinomas, surgical trauma, or CNS-involved leukemia. Patients with diabetes insipidus usually present with obvious symptoms of excessive thirst and urination with nocturia or enuresis. However, the diabetes insipidus may not be recognized until they have dehydration during an intercurrent illness. The urine remains clear in color throughout the day. In patients with CNS-involved leukemia, severe hypernatremic dehydration can occur if the CNS lesion also affects the centers for thirst regulation.

8.2 Osteopenia

Osteopenia in cancer survivors may be unrecognized in the absence of fractures unless evaluation is performed. Serum osteocalcin and urine pyridinoline crosslinks or N-telopeptide do not identify whether there is low bone mineral. Identification requires performance of a dual-energy X-ray absorptiometry (DXA) which offers precise estimates of bone mineral density (mg/cm^2) at multiple sites for the least amount of radiation exposure, or a quantitative computerized tomography (QCT) which measures true volumetric density (mg/cm^3) of trabecular or cortical bone at any skeletal site of choice. T-scores may be calculated in reference to normal young adults (age of peak bone mass, 20–35 years) and Z-scores in reference to age-matched normal individuals of the same gender, respectively. Results of DXA must be adjusted for patient height and age. T-scores should not be used in pediatric age patients.

Osteopenia may result from HPA abnormality (GH deficiency, hypothyroidism, hypogonadism, or hyperprolactinemia) in association with direct effects of glucocorticoid therapy, methotrexate inactivity, and dietary changes. Osteopenia may present with fractures or may be asymptomatic. Among 141 survivors of childhood leukemia in one study, 30 (21 %) had abnormally low bone mineral density (BMD > 1.64 SD below the mean of normal population). Risk factors for bone mineral decrement included male gender, Caucasian race, and cranial irradiation. BMD was inversely correlated with the cumulative dose of cranial irradiation or antimetabolites (Kaste et al. 2001).

There is increasing evidence that bone health is impaired in patients treated with combined modality therapy that does not necessarily include glucocorticoid therapy. Patients with Hodgkin lymphoma, for example, comprise a group of patients at risk for bone mineral deficits, among whom male patients were identified as those at increased risk (Kaste et al. 2009). Similar findings were noted for male patients with brain tumors (Morris et al. 2008). Osteonecrosis has been recognized as a late complication of therapy in adult

survivors of pediatric cancer (Kadan-Lottick et al. 2008). Osteonecrosis has also been shown to be an early complication of antiangiogenic therapy suggesting that endocrine-related effects may be part of the toxicity profile of newer treatments (Aragon-Ching et al. 2009).

8.3 Hypothalamic Obesity

Clinical symptoms are the basis for diagnosis of hypothalamic obesity. These include rapid weight gain, voracious appetite, and aggressive food seeking. Patients may have rapid weight gain for other reasons: exogenous steroid use, inactivity, overfeeding, and sympathy of relatives, high thirst and drinking of sugared drinks. Obesity in adults is defined as having a body mass index of >30 [BMI = wt(kg)/ht(m^2)] (http://nhlbisupport.com/bmi/). Overweight in children is defined as having a weight greater than the sex- and age-specific 95th percentile or BMI > 85th percentile (www.cdc.gov/growthcharts/). Evaluation of these patients includes blood pressure measurement, fasting lipid profile, fasting glucose and insulin level, and oral glucose tolerance testing with insulin levels (OGTT). In general, fasting glucose is normal and fasting insulin is elevated in patients with hypothalamic obesity. They have very high post-pyramidal insulin level as well as early and rapid insulin excursions to OGTT. However, these results may be seen in any person who becomes obese.

Hypothalamic damage from a tumor or cancer treatment can also result in hypothalamic obesity—unrelenting weight gain that does not respond to caloric restriction or exercise—attributable to ventromedial hypothalamus damage and abnormality in leptin, ghrelin, and insulin feedback (Lustig 2001). In rodents, hypothalamic obesity can be suppressed by pancreatic vagotomy to prevent insulin hypersecretion. Recent studies in patients with cranial insult confirmed insulin hypersecretion as one of the major mechanisms for the development of hypothalamic obesity (Lustig et al. 1999). In a study of 148 survivors of childhood brain tumors, the risk factors for hypothalamic obesity included age at diagnosis of cancer (<6 years), tumor location (hypothalamic or thalamic), tumor histology (craniopharyngioma, germinoma, optic glioma, prolactinoma, or hypothalamic astrocytoma), hypothalamic irradiation (>51 Gy), and presence of endocrinopathy (deficiency of GH, sex hormones, ACTH, or vasopressin) (Lustig 2001; Lustig et al. 2003b). No effects were noted on body mass index from ventricular peritoneal shunting, steroid use (<6 months), or chemotherapy. Thus, any form of hypothalamic damage, either due to tumor, surgery, or RT, is a regional-specific primary risk factor for the development of obesity in this patient population.

9 Prevention and Management

9.1 GH Deficiency

Standard therapy for GHD is synthetic recombinant human GH. Any patient identified with GHD should be evaluated for possible ACTH deficiency and for central hypothyroidism. If ACTH is deficient, adequate cortisol therapy should be started before GH or thyroid therapy. Patients with GHD who have partial or total ACTH deficiency and are receiving suboptimal hydrocortisone replacement may be at risk of developing symptoms of cortisol deficiency when GH therapy is initiated. This includes patients who are prescribed stress-dosing only of cortisol; they may need to receive daily replacement. This is because of the inhibitory effect of GH on 11β-hydroxysteroid dehydrogenase type 1, the enzyme that converts cortisone to cortisol (Toogood et al. 2000).

The usual dose of GH in children is 0.15–0.3 mg/kg per week divided into daily doses and administered subcutaneously in the evening. Lower doses are used in adults (Vance and Mauras 1999) and in countries such as the United Kingdom. Each dose produces a pharmacologic level of GH for approximately 12 h. The growth rate in children on GH therapy typically increases to above normal for 1–3 years and then slows to normal velocity. After 4–5 years of GH therapy, the height SD scores of leukemia survivors with GHD usually approached the height SD scores at the time of diagnosis (Leung et al. 2002). The growth response may be poorer in patients who have received total body or spinal irradiation, or in patients with particular diseases such as neuroblastoma (Olshan et al. 1993; Hovi et al. 1999). GH replacement helps many irradiated brain tumor patients to achieve mid-parental height. Patients treated with craniospinal irradiation or TBI are the least likely to achieve predicted height. Younger and short patients at the start of GH replacement therapy are also at risk (Beckers et al. 2010). Adult GH replacement studies show that irradiated patients had lower QOL and increased metabolic risks (higher fat mass, lower high-density lipoprotein cholesterol levels, and a lower bone mineral content) than nonirradiated patients (Maiter et al. 2006). There is great debate about the use of GH in adult cancer survivors. Many conclude that such survivors would benefit from GH replacement for body composition (Darzy and Shalet 2006). GH replacement may reduce cardiac risk factors (Follin et al. 2006). QOL may be improved in patients who receive GH replacement therapy. Those with severe GH appear to benefit most (Murray et al. 1999).

GHRH as therapy has been taken off the market in the USA. When available, GHRH may be used as an alternative

therapy for GH deficiency in patients without primary sellar tumors. GHRH therapy, also administered subcutaneously in daily evening doses, elicits a night-time pulsatile pattern of GH secretion that approximates the normal pattern. Experience with GHRH therapy after cranial irradiation is limited. In one study, nine children who had undergone cranial or craniospinal irradiation at least 2 years earlier were treated with twice daily subcutaneous injections of GHRH for 1 year, and then with daily GH injections for 1 year (Ogilvy-Stuart et al. 1997). Both GHRH and GH increased height velocity from baseline: GHRH increased height velocity from 3.3 to 6.0 cm/year, and GH increased it from 3.3 to 7.5 cm/year.

During GH therapy, evaluation of the growth response and adjustment of GH dose should occur every 4–6 months and include measurement of height, weight, and arm span. Arm span is a surrogate measure of height, particularly in patients in whom height measurement may not fully reflect body growth (e.g., those with scoliosis or a history of spinal irradiation). In most practice settings, GH dose is increased as weight gain occurs to maintain a stable dose per kilogram of body weight. Serum IGF-I measurements are recommended yearly (GH Research Society 2000). After the first 2 years of GH therapy, if the level of IGF-I surpasses the upper limits of normal for the patient's age and sex, the GH dose should be decreased. Evaluation of pubertal stage and screening for development of additional endocrinopathy (thyroid, gonadotropins, and ACTH) should be performed at least annually. Even with GH therapy, some childhood cancer survivors do not grow as well as expected. This finding suggests that other factors, such as thyroid hormone deficiency, are present.

The use and timing of GH replacement is an individual decision. Safety data has allowed us to administer GH earlier and gain time of exposure. When gain in height is critical, delay to GH affects final height (Brownstein et al. 2004). GH treatment in children is usually safe (Wilson et al. 2003). Adverse effects are rare, occur soon after therapy is initiated, and include pancreatitis, benign intracranial hypertension (pseudotumor cerebri), slipped capital femoral epiphysis, and carpal tunnel syndrome (Blethen et al. 1996). Pseudotumor cerebri and carpal tunnel syndrome are probably caused by sodium and water retention. An increase in the growth and pigmentation of nevi also has been described (Bourguignon et al. 1993). Tumor recurrence does not appear to be increased in patients treated with GH replacement therapy (Darendeliler et al. 2006; Chung et al. 2005). GH therapy also did not appear to increase the risk of secondary leukemia or solid malignancy in patients who did not receive RT in the Childhood Cancer Survivor Study (Sklar et al. 2002; Ergun-Longmire et al. 2006). Because all of the included patients who developed a second neoplasm in this study had received RT, the synergistic effects of GH and irradiation on the development of second malignancy could not be discerned (Sklar et al. 2002). The absolute number of excess solid tumors attributable to GH, including many benign meningiomas, will probably be very small (<4/1000 person years at 15 years after diagnosis).

9.2 Hypothyroidism

Standard treatment for TSH deficiency or for primary hypothyroidism is levothyroxine replacement therapy. Thyroid hormone replacement can precipitate clinical decompensation in patients with unrecognized adrenal insufficiency, because levothyroxine treatment may improve metabolic clearance of cortisol. Thus, it is necessary to evaluate patients for adrenal insufficiency, and if present, treat the patient with hydrocortisone before initiating thyroid hormone therapy. In patients who also have ACTH deficiency, cortisol replacement is usually initiated 3 days before beginning thyroid hormone therapy.

The typical thyroid hormone replacement dose for infants under 3 years of age is 5–10 mcg/kg per mouth daily. For healthy children and adolescents with TSH less than 30 mU/L, the typical thyroid replacement dose is levothyroxine 3 mcg/kg per mouth every morning. This should be started at full dose. Children over 3 years of age who have TSH greater than 30 mU/L, or about whom there are concerns about medical stability, can begin levothyroxine at a low dose (0.75 mcg/kg per mouth every morning) and have it increased by 0.75 mcg/kg per day each month to permit more gradual physiologic and psychologic adjustment to the new metabolic state. Thyroid hormone concentrations should be measured after 4 weeks of therapy, because levothyroxine has a long half-life (5–6 days).

Unlike primary hypothyroidism, it is not useful to monitor TSH in patients with central hypothyroidism. In one prospective study of 37 patients with central hypothyroidism, free T4 and free T3 were monitored during therapy and adjusted to achieve free T4 in the midnormal range without free T3 elevation and without symptoms of hypothyroidism or hyperthyroidism (Ferretti et al. 1999). We usually adjust thyroid hormone replacement therapy in patients with central hypothyroidism to maintain the level of free T4 just above the middle of the normal range (for example, free T4 of 1.4–1.6 ng/dL if the normal range is 0.78–1.85 ng/dL, free T4 of 1.8–2.2 ng/dL if the normal range is 1.0–2.4 ng/dL).

9.3 ACTH Deficiency

Patients with ACTH insufficiency require daily hydrocortisone replacement. Hydrocortisone is the preferred agent

for glucocorticoid replacement in children because it is least likely to impair growth. Patients with ACTH deficiency do not need mineral-corticoid replacement, because these hormones are produced by the adrenal gland under the influence of the renin-aldosterone system rather than under the influence of ACTH. Dexamethasone is not standard for glucocorticoid replacement therapy in the pediatric age range because it has greater potential to suppress growth than hydrocortisone. In adults, dexamethasone can be used for glucocorticoid replacement at a dose of 0.25–0.5 mg once each morning.

The dose of hydrocortisone for replacement therapy is 7–10 mg/m^2 per day, divided into two or three doses administered by mouth. For example, a child whose body surface is 0.9 m^2 could receive 2.5 mg three times per day, or an adult whose body surface is 1.5 m^2 could receive 5 mg at breakfast and at 1500 hours plus 2.5 mg at bedtime. The glucocorticoid dose may need to be increased in patients taking drugs, such as phenytoin, barbiturates, newer anticonvulsants, rifampin, mitotane, and aminoglutethimide that accelerate hepatic steroid metabolism (Elias and Gwinup 1980). Patients with GHD deficiency who have partial or total ACTH deficiency and are receiving suboptimal cortisol or cortisone replacement may be at risk of developing symptoms of cortisol deficiency when GH therapy is initiated. This is because of the inhibitory effect of GH on 11β-hydroxysteroid dehydrogenase type 1. Similarly, the initiation of thyroid hormone therapy in a child with unrecognized or under treated ACTH deficiency also can precipitate adrenal crisis.

Patients with ACTH deficiency must receive additional glucocorticoid during times of illness or stress (e.g., fever, gastrointestinal illness, injury, high-dose chemotherapy). Dexamethasone has no mineral-corticoid effect, so hydrocortisone should be used for stress dosing. The dose of additional hydrocortisone that is necessary during times of illness is 30 mg/m^2 per day divided into three doses administered by mouth. Patients whose illness or injury is severe enough to require emergency care or hospitalization, who are unable to retain oral medication, or who require anesthesia, surgery, or both should urgently receive hydrocortisone (100 mg/m^2 intramuscularly or intravenously), followed by hydrocortisone (10–25 mg/m^2 IV every 6 h) during management of the critical illness (Soule et al. 1996). At stress doses, hydrocortisone provides some mineral-corticoid effect. The hydrocortisone dose should be reduced to the usual replacement therapy dose as soon as the event is over or the patient's medical status improves. Tapering of the dose is not necessary if the pharmacologic stress doses are used for less than 10 days.

Patient and family education is an important component of treating patients with ACTH deficiency. The patient and responsible family members should be instructed about the following:

- The nature of the hormonal deficit and the rationale for replacement therapy
- Maintenance medications and the need for changes in medications during minor illnesses
- When to consult a physician
- The need to keep an emergency supply of glucocorticoids
- The proper *stress* dose for the patient's body weight
- When and how to inject glucocorticoids for emergencies.

Every patient should have at least three pre-prepared syringes of hydrocortisone (Solu-cortef®): one at home, one at work or school, and one in the car. In addition, it is wise for the patient to carry such a syringe at all times. The syringes can be obtained as 100 mg/2 mL vials, 250 mg/2 mL vials, or can be prepared by a pharmacist in regular 1-mL syringes from a multidose vial. The patient and parents must be instructed regarding the correct dose. The injectable stress dose is 5–10 times the daily hydrocortisone dose. Thus, typical doses for children would be 50–125 mg (0.4–1.0 mL of a 250 mg/2 mL solution). Unused syringes should be replaced each year or if the solution inside becomes cloudy or colored.

The patient and one or more responsible family or household members should be instructed to inject the contents of a syringe subcutaneously or intramuscularly anywhere on the patient's body during any one of the following circumstances:

- The patient has a major injury with substantial blood loss (more than one cup), fracture, or neurogenic shock
- The patient has nausea and vomiting and cannot retain oral medications
- The patient has symptoms of acute adrenal insufficiency
- The patient is found unresponsive.

Instructions should include the need to obtain medical help immediately after the injection of the stress dose. The patient should be instructed to have a low threshold for injecting the hydrocortisone: if the patient feels the injection *might* be necessary, then it *should* be injected, and medical attention should be sought. It is unlikely, however, that a patient will need the stress dose of hydrocortisone more than two or three times per year, and most patients go for years without needing it. Used hydrocortisone syringes should be replaced immediately.

Every patient should wear a medical alert (Medic Alert®) bracelet or necklace and carry the Emergency Medical Information Card that is supplied with it. Both should indicate the diagnosis, the daily medications and doses, and the physician to call in the event of an emergency. Patients can enroll in Medic Alert by calling 800-432-5372 or through the internet at www.medicalert.org (U.S.) or www.medicalert.ca (Canada).

9.4 LH/FSH (Gonadotropin) Deficiency

The use of estrogen or testosterone therapy should not be initiated without careful attention to the survivor's growth pattern. Replacement of pubertal hormones in a short or slowly growing adolescent can cause fusion of bony growth centers and shorter than expected adult height. Such therapy should be provided only in coordination with the pediatric endocrinologist after assessment of growth potential and treatment of GH or thyroid deficiencies. Initiation of sex steroid therapy in a short adolescent may be delayed until age 15 years to permit response to GH or thyroid hormone therapy and taller adult height. In short adolescents with delayed puberty, a few years of therapy with low-dose sex steroid therapy is preferable to full replacement. Such doses simulate the sex steroid levels observed in the first year or so of puberty and are less likely than full sex steroid replacement to cause inappropriate maturation of bone age. Girls can be treated with the conjugated estrogen tablets Premarin® (0.3 mg every other day), ethinyl estradiol (5 mcg daily, one quarter of a 20-mcg tablet daily), or one-fourth to one-half of an estrogen patch changed half as often as in adults (Rose 1996). Menstrual spotting can be treated with medroxyprogesterone 10 mg per day for 10 days followed by resumption of low-dose estrogen. Boys can be treated with 45 or 50 mg/m^2 depo testosterone injected intramuscularly once each month or with topical androgen gel about one gram daily. After achievement of height acceptable to the patient, both boys and girls benefit from a gradual increase in hormone replacement therapy to the full replacement dose, if there has been no sex steroid production in recent months. The increase to full replacement should take place in 1- to 3-month steps to permit gradual adjustment to the hormonal effects.

Full hormone replacement in adolescent girls who have reached their adult height is easily achieved with regular use of a standard oral contraceptive (28-day pill packet) or an adult regimen of estrogen patches plus progesterone. Boys who have attained their adult height can be treated with testosterone (200 mg injected intramuscularly every 2 weeks) with androgen by patch, or by topical gel.

The primary medical risk of delayed puberty is delayed bone mineralization. Adolescents with delayed or interrupted puberty should receive 1500 mg of elemental calcium and 1000–2000 IU of vitamin D per day to improve bone mineralization.

9.4.1 Precocious Puberty

GnRH agonists are the most effective treatments for precocious puberty, rapid tempo puberty, or normally timed puberty that is inappropriate relative to height. GnRH agonists suppress LH and FSH release from the pituitary gland through the provision of a steady rather than a pulsatile level of GnRH; the pituitary gland stops responding to GnRH when GnRH concentrations are steady or unchanging. The use of GnRH agonists to delay pubertal progression optimizes adult height potential by permitting the child to grow taller without experiencing a rapid change in bone maturation (Cassorla et al. 1997).

Treatment with GnRH agonists should be prescribed and monitored by a pediatric endocrinologist (Yanovski et al. 2003). GnRH agonists can be administered as a daily subcutaneous injection, every 4 weeks or every 3 months in a sustained or depot preparation or as a yearly implant. GnRH agonist therapy is usually continued until patients attain the third percentile for adult height: 152 cm (60 in.) in girls and 162 cm (64 in.) in boys.

9.5 Hyperprolactinemia

In event of a prolactin level in excess of 100 ng/mL, prolactin elevation may lead to symptoms (galactorrhea, amenorrhea, impotence). Dopamine agonists such as bromocriptine and cabergoline are the treatment of choice to suppress PRL secretion and to restore normal gonadal function. Cabergoline is, in general, more potent, much longer acting, and better tolerated than bromocriptine. The usual starting dose is 0.25 mg twice a week.

9.6 Diabetes Insipidus

The drug of choice for hormone replacement is desmopressin acetate or DDAVP®, which can be given by subcutaneous injection, by nasal insufflations, or orally in one or two daily doses. Oral desmopressin is available in tablets containing 0.1 or 0.2 mg. To avoid water intoxication, successive doses should not be given until a brief diuresis has occurred at least once daily. By giving a dose at bedtime, sleep disturbance by nocturia can be avoided. The usual dose of 1.25–5.0 μg intranasally, or 0.1–0.6 mg orally, will usually achieve rapid urinary concentration that lasts approximately 8–24 h. The process of starting desmopressin therapy may require close monitoring: volumetric fluid intake and urine output. Several weeks of dose adjustment may be required before achieving a stable dose. In patients with partial diabetes insipidus, chlorpropamide may be used to enhance the effect of the limited antidiuretic hormone that remains.

9.7 Osteopenia

Osteopenia after cancer therapy, including radiation and chemotherapy, and directly associated with multiple

endocrine deficiencies, may be prevented by maintaining optimal calcium (1500 mg daily) and vitamin D (1000 units daily) in the diet. Nutritional supplements may be needed in cases of osteopenia unresponsive to behavioral and dietary management. In addition, early diagnosis and replacement of hormone deficiencies will benefit bone mineralization. In the event of fractures, bisphosphonates may be beneficial. More aggressive measures have been investigated to prevent premature ovarian failure and address osteoporosis including ovarian transplantation (Feng et al. 2010).

9.8 Hypothalamic Obesity

Part of the therapy for hypothalamic obesity involves early identification and initiation of preventive measures including caloric and dietary control and maintenance of regular exercise. In addition to maintaining these lifestyle choices, pharmaceutical agents have been used pragmatically or in research efforts including Dexedrine, Ritalin, metformin, and octreotide. Dexedrine and Ritalin are taken orally and act as stimulants with the side effect of appetite suppression. Metformin is taken orally twice a day and acts as a sensitizer to insulin effects and may serve to probe the etiology of obesity in individual patients. If the obesity is exogenous, and hyperinsulinemia is a consequence of the obesity and insulin resistance, lifestyle changes with or without metformin will diminish obesity. If the obesity is hypothalamic and the hyperinsulinism is the cause of the increased appetite, metformin use may lead to hypoglycemia with no reduction in striving for food. Octreotide is a somatostatin analog that binds to the somatostatin receptor. It serves to decrease insulin secretion from pancreatic β-cells and GH and TSH secretion from the pituitary gland. If the obesity is exogenous and high insulin levels reflect insulin resistance, the patient may become diabetic with octreotide therapy. If the obesity is hypothalamic, octreotide will decrease insulin secretion leading to reduced appetite, weight control, and improved sense of well being (Lustig et al. 1999, 2003a, b). Octreotide is administered as 2 or 3 injections daily. Side effects may include gallstones and fluid retention. Patients treated with octreotide may also require therapy with GH and thyroid hormone.

Bariatric surgery has been used with mixed results to treat hypothalamic obesity in patients with craniopharyngioma (Rottembourg et al. 2009). Favorable outcomes have resulted in decreased food cravings and weight loss (Inge et al. 2007). It is critical to evaluate candidates carefully and determine that they have maximized life style conditions and have been thoroughly evaluated for treatable endocrine deficiencies.

10 Future Research Directions

In research efforts focused on improving our understanding of radiation and cancer treatment-related endocrine effects, baseline and longitudinal assessments should be prospectively planned and include, at a minimum, the somatic assessments of height, weight, and body mass index. More advanced research should address the impact of specific hormone deficiencies on QOL and be tailored to individual research effects seeking to determine the relationship between endocrinopathy and QOL, cognitive and neurological function, or biometric outcomes including neurostructural measures. Understanding radiation dose-volume effects on the hypothalamus-pituitary, thyroid, adrenal, and gonadal axes will serve to improve RT planning and delivery and measures to protect normal tissues. The same information will enable secondary prevention through early intervention. Collecting these data, now and in the future, will provide critical information to refine standard of care screening guidelines, reduce late effects and determine the benefit of old and new treatment methods including brachytherapy to hypo- and hyper-fractionated external beam irradiation and proton therapy.

The primary goal of radiation oncology is to achieve disease control with minimal side effects. Side effects may be attributed to a number of factors including the quality of RT and should be understood in the context of a multidisciplinary treatment approach. There are significant differences when considering the importance of endocrine effects in adults and children. With the exception of severe growth deformity that might result from craniospinal irradiation in a very young child, RT is generally not contraindicated when endocrine effects are considered treatable. Although the incidence and time to onset of hormone deficiencies should be the same for adults and children, there are number of differences between adult and pediatric oncology when endocrine management is considered. There is an emphasis in growth and pubertal development in children. In adults, including those transitioning from adolescent to adult, GH replacement therapy is often not undertaken or pursued because the relative risks and benefits have not been clearly understood. Often, the expense of treatment is a major barrier in a patient population that tends to be underemployed and underinsured. The prognosis may be better understood for children; however, there is a variety of tumor types and anatomic locations with a broad range of possible side effects. Age, duration since tumor therapy, and preexisting conditions are primary factors in development of late effects and differ between adults and children. Most pediatric patients receive polychemotherapy and most are

subject to long-term follow-up because survivorship is generally good. Current trends in pediatric oncology include increasing the indications for RT: younger patients are more likely to be irradiated and combined modality effects of therapy are now being recognized. The importance of the volumetric effect of radiation dose cannot be overlooked and must be considered in clinical trials and when developing treatment guidelines for adults and children.

11 Review of Literature and Landmarks

1954 Mateyko and Edelmann: Noted changes in gonadotropin, thyrotropin and adrenotropin 24 h after pituitary irradiation as above.

1957 McCombs: Presented a time-dose plot of the onset of changes resembling hypophysectomy induced by irradiation.

1959 Van Dyke et al.: Conducted an excellent study on the long-term effects of deuteron irradiation of the rat pituitary.

1960 Cleveland et al.: Made the latest metabolic analysis of proton irradiation of the pituitary. Ablative effects indicated that a fall in gonadotropins is the most sensitive index, followed by reduced thyroid and adrenal function.

1964: Tobias et al.: Analyzed pituitary endocrine alterations in humans after intense pituitary irradiation.

1968 Rubin and Cassarett: Presented the bio-continuum paradigm to chart clinical pathophysiologic events in an early/late timeline.

1995 Rubin: Presented the LENT-SOMA toxicity scales for radiation effects to evaluate the grade of severity.

2003 Trotti and Rubin: Modified and developed the Common Toxicity Criteria CTC V3.0 which applied similar scales to grade adverse effects of all major modalities—surgery and chemotherapy in addition to irradiation.

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