REVIEW

The hypothalamic–pituitary–adrenal axis in childhood cancer survivors

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Abstract

Endocrine abnormalities are common among childhood cancer survivors. Abnormalities of the hypothalamic–pituitary–adrenal axis (HPAA) are relatively less common, but the consequences are severe if missed. Patients with tumours located and/or had surgery performed near the hypothalamic–pituitary region and those treated with an accumulative cranial radiotherapy dose of over 30 Gy are most at risk of adrenocorticotrophic hormone (ACTH) deficiency. Primary adrenal insufficiency may occur in patients with tumours located in or involving one or both adrenals. The effects of adjunct therapies also need to be considered, particularly, new immunotherapies. High-dose and/or prolonged courses of glucocorticoid treatment can result in secondary adrenal insufficiency, which may take months to resolve and hence reassessment is important to ensure patients are not left on long-term replacement steroids inappropriately. The prevalence and cumulative incidences of HPAA dysfunction are difficult to quantify because of its non-specific presentation and lack of consensus regarding its investigations. The insulin tolerance test remains the gold standard for the diagnosis of central cortisol deficiency, but due to its risks, alternative methods with reduced diagnostic sensitivities are often used and must be interpreted with caution. ACTH deficiency may develop many years after the completion of oncological treatment alongside other pituitary hormone deficiencies. It is essential that health professionals involved in the long-term follow-up of childhood cancer survivors are aware of individuals at risk of developing HPAA dysfunction and implement appropriate monitoring and treatment.

Key Words

- ▶ ACTH
- ▶ cortisol
- ▶ HPA axis
- ▶ radiotherapy

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Introduction

Improvement in paediatric oncology treatment and support have overseen the dramatic increase in overall 5-year survival rates of all childhood cancers from less than 30% in the 1960s to the current >80% in the United Kingdom (<https://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/long-term-follow-up#heading=Two>). An estimated 1 in 640–700 young adults in the United States and United Kingdom is a childhood

cancer survivor (Campbell *et al.* 2004, Oeffinger *et al.* 2006). Unfortunately, survival comes with a cost, and there is ample evidence that childhood cancer survivors experience adverse physical, psychological and social health problems later in life, as well as premature mortality. Data from the United States, United Kingdom and Northern Europe have demonstrated a high relative risk of death with a standardised mortality rate of 8.3–10.8 in childhood cancer

survivors (Oeffinger *et al.* 2006, Mertens *et al.* 2008, Diller *et al.* 2009, Reulen *et al.* 2010, Garwicz *et al.* 2012). About three-quarters of patients were reported to have at least one chronic health condition and over two-fifths were affected by severe, disabling or life-threatening conditions or have died from chronic conditions within 30 years of diagnosis (Oeffinger *et al.* 2006).

In the United Kingdom, approximately 1800 new cases of cancer are diagnosed in children per year. Leukaemia is the most common childhood malignancy, followed by intracranial central nervous system (CNS) tumours and lymphoma. Other malignant conditions specific to children include neuroblastoma and nephroblastoma (Wilms' Tumour). As the population of childhood cancer survivors increases, emphasis on the management of the long-term health becomes more important with aims to prevent early morbidity and mortality. Around 50% of childhood cancer survivors develop one or more endocrine disorders with a higher risk among those treated for tumours of the CNS and the prevalence increases over time (Patterson *et al.* 2012, Brignardello *et al.* 2013, Mostoufi-Moab *et al.* 2016). Abnormalities of the hypothalamic–pituitary–adrenal axis (HPAA) are relatively less common in childhood cancer survivors compared with other endocrine disorders such as growth hormone deficiency, gonadal failure and hypothyroidism, but there can be a significant impact on morbidity and mortality risk (Rose *et al.* 2004). Under physiological stress, undiagnosed cortisol deficiency may present with life-threatening adrenal crisis. On a day-to-day basis, patients with adrenal insufficiency can experience subtle and non-specific symptoms such as fatigue, which are easily dismissed and result in a reduced quality of life.

This review provides an overview of risk factors, surveillance methods and future directions needed in the research of HPAA dysfunction in childhood cancer survivors under the following headings:

Risk factors for HPAA dysfunction:

1. The primary diagnosis: location and type of cancer
 - CNS tumours at the hypothalamic–pituitary (HP) region
 - Adrenal tumours
2. Treatment modality
 - Radiotherapy
 - o Accumulative dose and fractionation schedule
 - o Location – cranial irradiation to tumours in HP region and its proximity
 - o Location – cranial irradiation for malignancies not specifically involving the HP region or its proximity
 - Type of radiotherapy
 - Chemotherapy
 - Glucocorticoid therapy
 - Immunotherapy
 - Oncology treatment and autoimmune diseases

3. Patient factors

- Assessment of HPAA in childhood cancer survivors
- Relationship between HPAA function and wider aspects of health
- Future directions

Risk factors for HPAA dysfunction

Table 1 summarises key publications with data concerning HPAA dysfunction in childhood cancer survivors. The relevant studies are categorised according to the location of the primary tumour. However, the majority of the studies are limited by heterogeneity in patient characteristics such as the primary diagnosis, treatment modalities, age of treatment and follow-up time post treatment, as well as the method of assessment and definition of HPAA dysfunction.

The primary diagnosis: location and type of cancer

Unsurprisingly, tumours within or close to the HP region, and those of the adrenal glands can have a direct impact on HPAA function either as a result of the primary tumour or its treatment.

CNS tumours at the HP region

Intracranial tumours involving the HP region either directly or in its vicinity, such as the optic pathway, may result in central HPAA dysfunction at diagnosis as a result of local damage and/or after neurosurgery, with potentials for evolving effects over time from possible further tumour growth or after cranial irradiation (Fig. 1). Tumours at the suprasellar and intrasellar regions account for 10% of all CNS tumours in childhood (Arora *et al.* 2009). Abnormalities in endocrine function are often already present at diagnosis (Tan *et al.* 2017). The most common forms of childhood HP tumours are gliomas and craniopharyngiomas.

Gliomas – tumours derived from glial cells – are classified according to grade (low and high) and location. There is limited research distinguishing long-term sequelae caused by the tumour location from its treatment. Low-grade brain tumours such as HP low-grade astrocytoma may have an indolent course for many

Table 1 Summary of studies with data on HPAA function in childhood cancer survivors treated with radiotherapy.

Location	Reference	Primary diagnosis	Patient characteristics and treatment	HPAA diagnosis	Main outcomes on HPAA dysfunction
I. CNS tumours at HP region and vicinity	Gan et al. (2015)	Low-grade gliomas of optic pathway, hypothalamus, suprasellar	N=166 (76M) Dx: 4.9 (0.2–15.4) year FU: 8.3 (0.04–26.8) year RT: in all, CI: 48–55 Gy, 25–30#	ITT, SSST or LDST	<ul style="list-style-type: none"> ACTH deficiency: 13.3% Hypothalamic involvement implicated more than RT in onset of endocrinopathy and RT more of its density ACTH deficiency: 4.3%, 1% at diagnosis Median time of onset = 2.5 (0.01–7.0) year 5-year cumulative incidence: 2.9 (0.4–10.6)
II. CNS tumour outside the HP region	Clement et al. (2016b)	Low/high-grade glioma, DNET, medulloblastoma, sPNET, ependymoma, choroid plexus tumours, germ cell tumour, ATRT, others, without histology	N=718 (389M) Dx: 7.7 (0–17.7) year FU: 6.6 (2–13.4) year Age at FU: 15.1 (3.0–29.3) year RT: in 35.9% CI: 54.0 (12.5–60.0) Gy CS: 24.0 (18.0–39.7) Gy	ACTH deficiency definition: 'use of hydrocortisone maintenance or substitution documented'	<ul style="list-style-type: none"> Proton RT may reduce risk of some but not all late endocrine abnormalities ACTH deficiency in proton vs photons not significantly different (5 vs 8)%
	Eaton et al. (2016)	Medulloblastoma	Proton vs Photon respectively: N=40 (21M) vs 37 (24M) Dx: 6.2 (3.3–21.9) vs 8.3 (3.4–19.5) year FU: 5.8 (3.4–9.9) vs 7 year (3.5–13.5) RT (total): 54–55.8 Gy 100% vs 97.1% >55.8% Gy 0% vs 2.7% N=47 (26M) Dx: 8.5 (0.4–17.2) year FU: 2.4 (1.1–5.8) year RT: in number not stated, 9 with endocrine disorder all had CRT/CSI CI: 21–36 + 49.9–55.8 boost	08:00h cortisol and adrenal function testing (cut-off not specified)	<ul style="list-style-type: none"> 33 screened for endocrine disorder, 71% of this for HPAA function ≥1 endocrine problems in n=9 n=1 (medulloblastoma RT 36 + 54 Gy) had hypocortisolism, also had central hypothyroidism and GH deficiency 86% had data on HPAA, 43% of this ACTH deficiency with 4-year cumulative incidence 38 ± 6% ACTH deficiency not affected by dose of RT to hypothalamus
	Clement et al. (2014)	Low-grade glioma, medulloblastoma, sPNET ependymoma, others	N=88 (57M) Dx: 7.3 (3–20.1) year FU: 5.1 (2.1–9.6) year RT: CSI 23.4 (23.4–40.5) Gy, hypothalamus 44 (26.1–55.7) Gy, pituitary 42.1 (26.3–56.9) Gy	Cortisol: Morning (n=18) Random (n=37) Abnormal if LDST 20 min <18 µg/dL or metyrapone test 11DOC <7 ng/dL	
	Laughton et al. (2008)	Supratentorial (ATRT, pineoblastoma, PNET) Infratentorial (ATRT, medulloblastoma, PNET)			

(Continued)

Table 1 Continued.

Location	Reference	Primary diagnosis	Patient characteristics and treatment	HPAA diagnosis	Main outcomes on HPAA dysfunction
	Schmiegelow <i>et al.</i> (2003)	'Brain tumours not directly involving HP axis' (astrocytoma, medulloblastoma, ependymoma, germ cell tumour, glioma, pinealoma, haemangiopericytoma, PNET and non-histological verified) diagnoses	N=73 (46M) Age at RT: 8.4 (0.8–14.9) year FU: median 15 (2–29) year Age at FU: 21.6 (6.2–43.5) year RT: All had CI or CSI BED to HP region: 73 (0–94) Gy	ITT SSST	<ul style="list-style-type: none"> N=14 (19%) suboptimal cortisol in synacthen and ITT 10/33 (30%) passed SST but failed ITT 13 failed SST at 30min passed 60min n=33 had ITT, 48% failed peak cortisol Best fit model for failed ITT included: BED ($P=0.04$), length of f/u ($P=0.06$) ITT gold standard HPAA Abnormalities developing over time 1 with abnormal cortisol response on both test was subsequently diagnosed with late onset congenital adrenal hyperplasia n=2 with suboptimal cortisol at second ITT had normal baseline cortisol, and subsequent LDST showed normal peak and increment n=2 borderline cortisol response to second ITT had normal 08:00 h cortisol and increment response to LDST No abnormalities HPAA
	Spoudeas <i>et al.</i> (2003)	Posterior fossa tumour	N=16 (12M) Age at diagnosis: 5.7 (2.5–8.8) year FU: 11 (6.8–21.4) year Age and no of years after RT respectively: 1st test: 1.3 (0.5–2.5) and 9.2 (6.5–14.6) year 2nd test: 7.7 (5–10.1) and 15.7 (12.3–26.1) year RT: 30 Gy, 18–20#, 20-y boost, BED to HP 77.4 (70.8–91.7) Gy	ITT x 2 Pre-pubertally and at the end of growth	
	Heikens <i>et al.</i> (1998)	Medulloblastoma	N=20 (14M) Dx: 9.2 (5–17) FU: 16 (8–25) year Age at FU: 25 (19–33) year RT: 35±2.6 Gy, boost 18±3.7 Gy	ITT	
III. Mixed CNS tumours at HP region and vicinity and outside the HP region	Ramanauskienė <i>et al.</i> (2014)	Glioma (including optic nerve), medulloblastoma, PNET ependymoma, intracranial germ cell tumour, unidentified	N=51 (32M) Dx: 7.9 (0.25–17.2) year FU: 21 month (0.25–10.6) year RT: of 56.9% CI 44.8%, CSI 55.2% Dose: 54.2 (45–60) Gy	Morning cortisol <10:00 h at 138 nmol/L	<ul style="list-style-type: none"> Cortisol deficiency in 4.2% after mean 83.4 month (95% confidence interval 71.7–95.5)

Shalitin <i>et al.</i> (2011)	Optic glioma medulloblastoma astrocytoma ependymoma germinoma, others	N=114 (68M) Age at FU: 15.57 ± 5.93 year Dx: 7.07 ± 5.42 years FU: 12.8 ± 6.25 years RT: CI 48.2%, CSI 23.7% Dose: CI: 35–56 Gy, CSI: 30–54 Gy	SSST (peak cortisol level <54 nmol/L)	<ul style="list-style-type: none"> Endocrine abnormality n=57 (50%) % hormone deficits increases with time hypocortisolism n=9 ACTH deficiency increased (but not statistically significant) with: cranial radiation (12.7 vs 3.4%) and suprasellar location (16.2 vs 3.9%) ACTH deficiency not significantly different between groups: <ul style="list-style-type: none"> proton therapy (n=3) Proton plus conventional therapy (n=3)
Viswanathan <i>et al.</i> (2011)	Craniopharyngioma, medulloblastoma, glioma, RMS, ependymoma, astrocytoma, PNET, retinoblastoma, glioblastoma, germinoma, Ewing sarcoma	N=38 (19M) Age at FU mean: 11.9 ± 3.3 year FU: 1.8 ± 0.8 year RT: Proton (n=19, dose 5384 ± 268 cGy) vs proton plus conventional RT (n=12, dose 5775 ± 226 cGy)	LDST (peak cortisol <18 µg/dL)	<ul style="list-style-type: none"> 2 (9%) patients failed LDST, 3 (14%) failed SSST, 5 (23%) failed ITT, 5 (23%) failed Metyrapone test All failed the Metyrapone test had low basal cortisol responses. ACTH abnormal in 11/31 (35%) patients
Shankar <i>et al.</i> (1997)	Craniopharyngioma, medulloblastoma, optic glioma, NPC, ependymoma, PNET, undifferentiated carcinoma, Rathke cleft cyst, RMS, germ cell tumour	N=22 FU: 48 (16–167) month RT: n=18 had >3600 cGy to HP	Basal cortisol levels LDST SSST ITT Metyrapone test	<ul style="list-style-type: none"> 4/90 patients had abnormal cortisol response
Constine <i>et al.</i> (1993)	Glioma, medulloblastoma, ependymoma, others (unspecified)	N=32 (16M) Dx: 19 (2–57) year Age at FU: 26 (6–65) year FU: 7 (2–13) year RT: HP dose 53.6 (39.6–70.2) Gy CS: 31 (18–29.6) Gy (n=9)	Metyrapone test	
Livesey <i>et al.</i> (1990)	Medulloblastoma, astrocytoma, ependymoma, glioma, optic nerve glioma, pineal tumour, neuroectodermal tumour, meningioma, oligodendroglioma	N=144 (76M) Dx: 6.7 (1.3–15) year FU: 9.6 (2–26) year RT: HP 48 (10–56) Gy, CS 20 (25–33) Gy	ITT	
Mostoufi-Moab <i>et al.</i> (2016)	Leukaemia, HL, CNS tumours (unspecified), Wilms, soft tissue sarcoma, bone, NHL, neuroblastoma	N=14,290 (7675M) Dx: 6 (<1–20) year FU: 24 (5–39) year Age at FU: 32 (5–58) year RT brain: 0–18 Gy 33%, 18–30 Gy 21%, >30 Gy 12%	ACTH deficiency definition: 'regularly taking steroids to replace body hormones'	<ul style="list-style-type: none"> ACTH deficiency Hazard ratio=4.5; 95% (CI: 3.7–5.5)
Chemaitilly <i>et al.</i> (2015)	Leukaemia, lymphoma, CNS tumours unspecified, embryonal, bone and soft tissue, carcinoma, others	N=748 (394M) Age at RT: 7.6 (0.1–26) year FU: 27.3 (10.8–47.7) year Age at FU: 34.2 (19.4–59.6) year RT: CI <15 Gy-5.3%, 15–21.9 Gy-27.8%, 22–22.9 Gy-42.3%, 30–39.9 Gy-4.1%, >40 Gy-20.5%	08:00 h Cortisol <5 µg/dL (135 nmol/L)	<ul style="list-style-type: none"> 4% for ACTHD (13.3% if >40 Gy, 1.7% if <40 Gy) Higher odds with ACTHD if time since CRT <15 year <ul style="list-style-type: none"> CRT dose >30 Gy

(Continued)

Table 1 Continued.

Location	Reference	Primary diagnosis	Patient characteristics and treatment	HPAA diagnosis	Main outcomes on HPAA dysfunction
	Brignardello <i>et al.</i> (2013)	Haematological (ALL, HL, NHL, AML), brain tumours unspecified, sarcoma, others	N=310 (M=180) Dx: 9.97 (7.29) year FU: 16.09 (9.5) year Age at FU: 24.89 (7.4) year RT: any 64.4%, CI 23.9%, TBI 12.9% Dose unclear 12–64 Gy if GHD N=78 (56% M) Dx: 6.5 year FU: 6.8 (±4.3) year RT: in 67.9%, 10–19.9 Gy n=12, 20–29.9 Gy n=17, 30–39.9 Gy n=8, >40 Gy n=12	Morning cortisol and ACTH, provocation test (not specified) if baseline abnormal with risk factors/symptoms	<ul style="list-style-type: none"> Central hypoadrenalism n=4
	Patterson <i>et al.</i> (2009)	Medulloblastoma, leukaemia/lymphoma, craniopharyngioma, neuroblastoma, nasopharyngeal RMS, other brain tumours, pineal tumour, pituitary adenoma, other solid tumours, histiocytosis, Juvenile pilocytic astrocytoma, optic nerve glioma, haematological disorder		LDST >500 nmol/L SSST >500 nmol/L 08:00 h cortisol >365 nmol/L	<ul style="list-style-type: none"> Adrenal insufficiency diagnosed by LDST in 35%, SST in 11% 68% failed the LDST had normal SST 63% agreement between 8 am cortisol and LDST Adrenal insufficiency (LDST) vs RT: 83% >40 Gy, 50% 30–39.9 Gy, 12% 20–29.9 Gy, 8% <20 Gy Recommend LDST not 08:00 h cortisol in patients >30 Gy ACTH deficiency in n=56 (18%): 28% >24 Gy, 9% 14–24 Gy, 53 (95%) received mean CI 45.5 (14–70) Gy 3 ACTH deficiency without CI were diagnosed with craniopharyngioma, hypothalamic astrocytoma, and brain stem glioma 12/17 suboptimal cortisol response Survivors vs controls: no differences in ACTH No association between ACTH or cortisol response to time elapse from treatment or CI dose Endocrine dysfunction n=24 (30%), ACTH deficiency in N=3 (4%) after 6.6 (2.5–8.7) year FU
	Rose <i>et al.</i> (2005)	Craniopharyngioma, other suprasellar, medulloblastoma, other posterior fossa, supratentorial tumour, head and neck non-CNS tumour, haematological, torso solid tumours	N=310 FU: 6.1 ± 4.1 year RT: in 151/200 CNS tumours, 74/97 haematological malignancies Dose: 31 ± 23 Gy (0–74)	Both LDST and metyrapone test (66%) Metyrapone only (28%), LDST only (6%)	
	Oberfield <i>et al.</i> (1997)	Acute leukaemia or brain/head and neck tumours distant from HP	N=17 (M=5) Dx: 3.75 (1.5–19) year FU 5 (0.1–20) year RT: dose to HP 18–72 Gy (>33 Gy except 1)	CRF test	
V. Non-CNS	Clement <i>et al.</i> (2016a)	RMS at parameningeal/orbit/orbit and parameningeal/head, neck nonparameningeal	N=80 (M=52) Dx: 5.2 (0–13.6) FU: 11.8 (2.4–22.9) year RT: Initial (N=63), 45 (36–57.75) Gy Recurrence (N=17), 45 (40–60) Gy	Not specified	

Follin <i>et al.</i> (2014)	ALL (with CI)	N=44 (23M) Dx: M-4.4 (1.9–17.2), F-4.1 (1.1–13.2) year FU: 20 (8–27) year Age at FU: 25.5 (2–32) year RT: all had CI 24 (18–30) Gy, 1.7 (1–2)#	ITT, normal peak cortisol >500 nmol/L	<ul style="list-style-type: none"> 14/44 (32%) ITT sub-normal peak cortisol (257–478 nmol/L, ref >500 nmol/L) Survivors vs controls: no differences in basal cortisol
		N=519 (266M) Dx: 4.8 (3.9) year FU: 7.2 (3.7) year Age at FU: 12.1 (4.4) year RT: any 38.5%, CI 15.2%, TBI 8.1%, ?dose	RT >40 Gy screened by morning cortisol and if abnormal LDST/SSST Symptomatic patients with LDST/SSST	<ul style="list-style-type: none"> 480 endocrine conditions in 299 survivors (57.6%) N=6 (1.2%) with adrenal insufficiency
Patterson <i>et al.</i> (2012)	ALL, AML, NHL, HL, sarcoma, neuroblastoma, Wilms, others			
Crowne <i>et al.</i> (1993)	ALL (with CI)	N=20 (11M) Dx: 3.6–10 year FU: 3.6–10 year Age at FU: 6.9–18.2 year RT: all had 18.9 (18–24) Gy, 10–12#	ITT 24h ACTH and cortisol profiling 20-min intervals	<ul style="list-style-type: none"> ITT: normal peak cortisol responses Profiles: normal preserved circadian rhythm

ACTH, adrenocorticotrophic hormone; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ATRT, atypical teratoid rhabdoid tumour; BED, biological effective dose; CI, cranial irradiation; CRF, corticotropin-releasing hormone; CS, craniospinal irradiation; DNET, dyssembryoplastic neuroepithelial tumour; Dx, age at diagnosis; F, female; FU, follow-up (since end of treatment); GH, growth hormone; HL, Hodgkin's lymphoma; HP, hypothalamic-pituitary; ITT, insulin tolerance test; LDST, low-dose Synacthen test; M, male; NHL, non-Hodgkin's lymphoma; NPC, nasopharyngiocarcinoma; PNET, primitive neuroectodermal tumour; RMS, rhabdomyosarcoma; RT, radiotherapy; sPNET, supratentorial primitive neuroectodermal tumour; SSST, standard Synacthen stimulation test; #, fractions; ?dose, unspecified dose.

years with potential for progressive HP dysfunction. Gan *et al.* reported adrenocorticotrophic hormone (ACTH) deficiency in 13.3% of 166 cases of childhood glioma affecting the optic pathway, hypothalamus, suprasellar region and crucially demonstrated hypothalamic involvement or the presence of diencephalic syndrome as key predictors of the onset of most endocrine dysfunction (Gan *et al.* 2015). Diencephalic syndrome, in particular, was reported as an independent positive predictor for ACTH deficiency with a hazard ratio of 15.7. Reversible HPAA dysfunction was found in two patients possibly secondary to dexamethasone suppression (Gan *et al.* 2015).

Craniopharyngiomas are suprasellar tumours derived from embryonic tissues and may present with endocrine abnormalities such as growth failure and pubertal disorders even before surgical interventions. ACTH deficiency in childhood survivors of craniopharyngiomas is common after surgery, but the prevalence has reduced more recently as treatment preference moves towards less invasive surgery with the use of adjuvant therapies such as radiotherapy and chemotherapy. Cohen *et al.* compared endocrine outcomes of childhood craniopharyngioma survivors diagnosed over a 30-year period and reported a lower, but still substantial prevalence of ACTH deficiency of 64% at follow-up in those diagnosed between 2001 and 2010 compared with 95% from 1991 to 2000 (Cohen *et al.* 2013).

HPAA dysfunction may also occur in patients with non-CNS cranial tumours at close proximity to the HP region (e.g. rhabdomyosarcoma at the orbital and nasopharynx) and brain tumours distant from the HP region (e.g. medulloblastoma) as a result of their treatment. This is discussed later under treatment modality.

Adrenal tumours

Primary adrenal tumours are very rare in children, but it is key to establish the extent of any surgery involving the adrenal glands or abdominal masses, which could involve adrenals. Surgical resection of one or both adrenals may occur in the management of neuroblastoma, nephroblastoma and pheochromocytoma. Neuroblastomas (primary adrenal medulla tumours), which originate from immature neuroblasts and secrete catecholamine precursors, are treated by surgery and radiotherapy, with the addition of chemotherapy and autologous stem cell rescue if metastasis is present. Nephroblastomas are associated with an abnormal proliferation of embryonic kidney cells (metanephroma)

Figure 1

Common sites for cranial tumours in children who are commonly treated with radiotherapy.

and may present as a large abdominal mass, treated primarily by surgery, i.e. nephrectomy, which may also include adrenalectomy, followed by chemotherapy. Post-operative radiotherapy to the flanks is given to cases with incomplete resection or metastasis. Normal adrenal function with compensatory increase in baseline ACTH and cortisol levels had been demonstrated in childhood survivors of neuroblastoma and nephroblastoma after unilateral adrenalectomy (van Waas *et al.* 2012), but there are limited data on the effects of abdominal irradiation on the adrenal glands (Bölling *et al.* 2010). Childhood adrenocortical carcinoma is very rare and may be sporadic or part of a genetic syndrome such as Carney Complex, Li Fraumeni and MEN type 1. The risk of cortisol deficiency after surgical resection, or additional treatment with chemotherapy, radiotherapy and hormone therapy is obviously significant and requires investigation.

Treatment modality

In addition to the direct effects from tumour destruction and surgical resection, other treatment modalities such as radiotherapy, chemotherapy and immunotherapy may also lead to endocrine dysfunction. Radiotherapy is the most commonly implicated treatment modality in long-term HP dysfunction, and its effects are known to be dose and schedule dependent. This applies not only to tumours in the HP region, but also those in the vicinity or further away where the bio-equivalent dose (BED) to the HP region is inevitably still significant. There is limited evidence of any effect on HPAA function from adjunct standard chemotherapy, but emerging evidence of significant endocrine problems after immunotherapy.

Radiotherapy

The impact of radiotherapy on the HP axis is well established. Compared with other pituitary hormone axes, the HPAA is more resistant to radiation-induced damage. Nevertheless, the risk of HPAA dysfunction is not negligible as studies specific to survivors treated with cranial irradiation have reported a prevalence of up to 43% (Laughton *et al.* 2008) (Table 1). The risk of HPAA dysfunction is associated with the accumulative dose, fractionation schedule, location and type of radiation. Current recommended radiotherapy regimens of the common paediatric tumours in the United Kingdom are summarised in Table 2 (British Neuro-Oncology Society 2011, Royal College of Radiologists 2016). The biological effects of different radiation schedules can be quantified more precisely by linear quadratic model mathematically to calculate the BED of irradiation and therefore assessment of the impact to specific tissues such as the hypothalamic and/or pituitary function (Schmiegelow *et al.* 2000, Jones *et al.* 2001). However, this information is not always available.

Accumulative dose and fractionation schedule The risk of HP dysfunction post cranial irradiation is dose dependent and increases with increased accumulative dosage. The Childhood Cancer Survivor Study showed that ACTH deficiency occurred significantly more often after hypothalamic irradiation of greater than 30Gy compared with survivors exposed to 0–30Gy, with a hazard ratio of 4.5 (95% CI, 3.7–5.5) (Mostoufi-Moab *et al.* 2016). In a mixed cohort of survivors treated with cranial irradiation, Patterson *et al.* showed increased prevalence of abnormal adrenal function by low-dose Synacthen test with progressive increase in radiation dose: 8%:

Table 2 Radiotherapy dose and fractionation schedules of common childhood cancers.

Site	Malignancy	Dose	No of fractions # (over weeks/days)
CNS	Low-grade astrocytoma ^a	54 Gy	30# (6 week)
		Spinal: 50.4 Gy	28# (5.5 week)
	High-grade astrocytoma ^a	<14 year: 54 Gy	30# (6 week)
		>14 year: 60 Gy	30# (6 week)
	Ependymoma ^a	59.4 Gy	33# (6.5 week)
	Medulloblastoma ^a	Standard risk: Medulloblastoma/PNET	
		23.4 Gy + boost to tumour bed/posterior fossa	13# (2.5 week)
		30.6 Gy	17# (3.5 week)
		High risk medulloblastoma and Supratentorial PNET:	
		36 Gy	20# (4 week)
		39.6 Gy (M2-3)	22# (4.4 week)
		Boost to primary sites: 54–55.8 Gy	in 1.8 Gy
		Boost to metastatic sites: 50.4 Gy (spinal) 54–55.8 Gy (intracranial)	in 1.8 Gy
		No chemotherapy:	
		24 Gy	15# (3 week)
		16 Gy	10# (2 week)
		Post chemotherapy: 24 Gy	15# (3 week)
		Boost to residual disease 16 Gy	10# (2 week)
		Non-germinomatous 54 Gy	30# (6 week)
Orbit/nasopharynx	Rhabdomyosarcoma ^a	Meningeal metastasis 30 Gy	20# (4 week)
		Brain stem glioma ^a 54 Gy	30# (6 week)
		Craniopharyngioma ^a 50–55 Gy or 52.2–54 Gy	30–33# (6–6.5 week)
			27–28# (5.5 week)
		Embryonic: No surgery	
		Complete response to chemotherapy: 41.4 Gy*	23# of 1.8 Gy
		Incomplete response to chemotherapy: 50.4 Gy*	28# of 1.8 Gy
		Surgery: 36 Gy	20# of 1.8 Gy
		Alveolar No surgery: 50.4 Gy*	28# of 1.8 Gy
		Surgery: 41.1 Gy	23# of 1.8 Gy
		*±5.4 Gy for large tumours/poor response	3# of 1.8 Gy
		Brain: 35 Gy	21# of 1.67 Gy
		Spine: 35 Gy	21# of 1.67 Gy
		Boost for metastasis Intracranial: 20 Gy	12# of 1.67 Gy
		Spinal metastatic: 15 Gy	9# of 1.67 Gy
Leukaemia	Leukaemia (cranial) ^a	24 Gy	15# (3 week)
	Leukaemia (TBI for HSCT) ^a	14.4 Gy	8# (4 day)
	Leukaemia (CNS cranial boost) ^a	5.4 Gy	3# (3 day)
Abdominal	Neuroblastoma ^a Wilms tumour ^a	21 Gy	14# (3 week)
		Intermediate risk: 14.4 Gy	8# (1.5 week)
		High risk 25.2 Gy	14# (2 week)
		Whole abdomen 21 Gy	14# (2 week)
		Boost to macroscopic disease/nodes: 10.8 Gy	6# (2 week)
		Whole lung: 15 Gy	10 (2 week)

^aRoyal College of Radiologists (2016); ^bBritish Neuro-Oncology Society (2011).

<20 Gy, 12%: 20–29.9 Gy, 50%: 30–39.9 Gy, 83%: >40 Gy (Patterson *et al.* 2009).

Radiation-induced toxicity is also dependent on the fractionation schedule that is the fraction size and the time allowed between fractions for normal tissue to repair (Mostoufi-Moab & Grimberg 2010). Most radiation schedules use less than 2 Gy per fraction and no more than 5 fractions per week to minimise the damage to healthy neuronal tissues. Higher radiation doses of >2 Gy per fraction (for the same total dose) can induce relatively more injury to the later-responding (neuronal) than the early-responding (tumour) tissues (Darzy & Shalet 2009). However, previous trials comparing hyper-fractionated (e.g. splitting the usual radiotherapy dose to twice a day) with conventional radiotherapy regimens in paediatric oncology have not shown a difference in late toxicity (Paulino 2013).

Location – cranial irradiation to tumours in HP region and its proximity Cranial radiotherapy is widely used in the treatment of HP brain tumours and non-CNS cranial solid tumours in its proximity (e.g. orbital, nasal, pharyngeal rhabdomyosarcomas) (Fig. 1 and Table 1). Typical doses of cranial radiotherapy are 30–50 Gy over 3–5 weeks depending on the diagnosis and extent of the disease, and additional radiation ('boost') doses may be required in some metastatic tumours or residual disease post neurosurgery (Table 2). The effects of the total accumulative dose are high enough to result in HP dysfunction including ACTH deficiency in some patients (Clement *et al.* 2016a).

Gan *et al.* reported primary radiotherapy as an independent predictor for ACTH deficiency in tumours affecting the hypothalamus and its vicinity with a hazard ratio of 5.2 (Gan *et al.* 2015). A high risk of HPAA dysfunction is expected in childhood cancer survivors with tumour involving at the HP gland directly, studies have also shown that CNS tumours in the vicinity of the HP region (Fig. 1) also involve a significant BED to the HP region (Table 1).

Location – cranial irradiation for malignancies not specifically involving the HP region or its proximity Cranial irradiation that is given to some malignancies outside the HP region may still have a significant impact on HP function. Whole brain radiotherapy is delivered in high doses to a number of non-HP CNS tumours. Cranial irradiation of 18–24 Gy was also given routinely in the past to children with acute lymphoblastic leukaemia as prophylaxis against

CNS relapse, but this is now reserved for cases with CNS disease. Total body irradiation of 10–16 Gy in 3–8 fractions is used as part of conditioning prior haematopoietic stem cell transplantation (HSCT) in some haematological malignancies such as acute lymphoblastic leukaemia. There is a large variation in the prevalence of HPAA dysfunction from such radiotherapy dose to the HP region reported in the literature, which is largely depending on the study population (Fig. 1 and Table 1).

Section II in Table 1 shows outcomes of ACTH deficiency in studies of CNS tumours not involving the HP region, but treated with radiotherapy. Laughton *et al.* reported a significant 43% prevalence of ACTH deficiency using the low-dose Synacthen stimulation test (LDST) in a mixed cohort of supra and infratentorial tumours distant from the HP region treated with a HP radiation BED of >40 Gy (Laughton *et al.* 2008). Schmiegelow *et al.* reported suboptimal cortisol response by insulin tolerance test (ITT) or LDST in 19% of childhood cancer survivors with brain tumours not directly involving the HP axis at a median follow-up of 15 years, who were treated with a BED of 73 (0–94) Gy to the HP region (Schmiegelow *et al.* 2003). However, ACTH deficiency was less common in other studies. Spoudeas *et al.* reported 3 out of 16 survivors of posterior tumour fossa tumours with suboptimal peak cortisol repose by ITT after 15.7-year follow-up, but one was later diagnosed with congenital adrenal hyperplasia and the other 2 had normal basal cortisol responses and subsequent normal results from LDST (Spoudeas *et al.* 2003). Heikens *et al.* also reported no cases of HPAA dysfunction among 20 childhood survivors of medulloblastoma by ITT (Heikens *et al.* 1998). It is difficult to extrapolate outcomes from some studies, which include mixed patient cohorts treated with and without radiotherapy (Clement *et al.* 2014, 2016b) and others with both HP and non-HP CNS tumours and/or non-CNS tumours, which did not report outcomes separately according to tumour location (Table 1, section III and IV).

The other main group of non-HP malignancies treated with cranial irradiation are the historical survivors of childhood lymphoblastic leukaemia (Table 1, section V). The risk of HPAA dysfunction of this group is multifactorial such as the time elapsed from treatment, dose of radiation and fractionation. Crowne *et al.* did not show the presence of ACTH deficiency after 4–10 years of follow-up (Crowne *et al.* 1993), whereas a high prevalence of 14/44 (32%) was reported in survivors 20 years post treatment by Follin *et al.* (2014). However, survivors in the latter study received significantly higher doses of CI

in fewer fractions (Follin *et al.* vs Crowne *et al.* = 24 Gy in 1–2 fractions vs 18.9 Gy in 10–12 fractions, respectively; Crowne *et al.* 1993, Follin *et al.* 2014).

Type of radiotherapy Radiotherapy for cancer treatment involves the use of ionising radiation to kill or stop the replication of cancer cells. The most common modality of external beam radiation therapies are electromagnetic rays (i.e. photon beams from X-rays and gamma rays) and particle radiation (i.e. protons, neutrons, electrons) generated by linear acceleration.

Until recently, photon beams have been most widely used in the treatment of childhood cancer. Energy from photons deposit dose along the entire beam path where maximum dose is delivered just below the skin surface and continues until it exits the body. The newer proton radiotherapy uses protons, the positively charged particles from the atomic nucleus. Proton beams deliver the maximum dose of radiotherapy at the end of the path in a well-defined peak localised to the tumour (known as Bragg peak). There is minimal amount of energy deposited along the rest of the path, which therefore reduces radiation exposure to large volumes of normal tissues (Fig. 2).

Data comparing the long-term outcomes in childhood cancer survivors treated with proton therapy with conventional therapy are beginning to emerge. Eaton *et al.* (2016) investigated the prevalence of endocrine abnormalities in 77 children with medulloblastoma who were treated with chemotherapy and proton ($n=40$) or photon ($n=37$) radiation with median follow-up of 5.8 and 7 years. The study found that proton radiotherapy may reduce the risk of some, but not all radiation-associated late endocrine abnormalities. ACTH deficiency was reported in

5% of the cohort, which was not statistically different to those who had conventional photon therapy (Eaton *et al.* 2016). In a study with a mixed cohort of CNS tumours, Viswanathan *et al.* compared 19 patients who had proton therapy with 12 conventional plus proton therapy, and reported ACTH deficiency in three patients in each group by LDST (Viswanathan *et al.* 2011). Abnormalities were detected sooner during follow-up in the conventional radiotherapy plus proton therapy group than in the proton therapy only group (Viswanathan *et al.* 2011).

Chemotherapy

Chemotherapy-related transient HPAA dysfunction is reported in the acute periods of treatment in some childhood cancers, but evidence of its long-term effects is minimal.

Published data have shown that HPAA dysfunction is uncommon in childhood cancer survivors of CNS tumours treated without cranial or total body irradiation. Schmiegelow *et al.* compared HPAA function via ITT and ACTH test in 73 childhood brain tumours with 17 controls and concluded no additional effect from chemotherapy to the impact of cranial irradiation (Schmiegelow *et al.* 2003). Cochrane *et al.* reported no cases of cortisol deficiency among 30 childhood cancer survivors with CNS tumours treated with radiation avoiding therapies after a mean of 8 years (Cochrane *et al.* 2017).

Among survivors of chemotherapy-treated non-CNS tumours, HPAA insufficiency is also rare with the exception of drugs used to treat malignant adrenocortical tumours (e.g. mitotane), which can lead to adrenal necrosis and glucocorticoid and mineralocorticoid deficiency. In a cohort of 31 childhood cancer survivors with non-CNS disease treated with chemotherapy only, Rose *et al.* reported 81% developed one or more endocrine abnormalities 13 years post treatment, but none had ACTH deficiency (Rose *et al.* 2004).

Glucocorticoid treatment

Secondary adrenal insufficiency is common in childhood cancer survivors after prolonged high doses of glucocorticoid therapy and may persist for some time even if treatment is withdrawn gradually. Glucocorticoids are used as part of the treatment protocol for some malignancies such as acute lymphoblastic leukaemia and lymphoma. It may also be given to relieve side-effects of chemotherapy such as vomiting, reduce inflammation such as cerebral oedema associated with intracranial neoplasms and treat graft-vs-host disease after HSCT.

Figure 2
Radiation effects from photon vs proton radiotherapy.

Transient steroid-induced hypoadrenalism has been reported in up to 67% of acute lymphoblastic leukaemia survivors post induction and may persist for 8.5 months and longer (Vestergaard *et al.* 2011). The latest Cochrane review on adrenal insufficiency in childhood acute lymphoblastic leukaemia after glucocorticoid therapy included 10 studies with 298 patients, reported adrenal insufficiency in nearly all children in the first days after cessation of glucocorticoid treatment. While the majority recovered within 7 weeks, a small number of children had ongoing adrenal insufficiency lasting up to 34 weeks. High-dose fluconazole was suggested as a risk factor for prolonged adrenal insufficiency. The relationship between the presence of infection or stress and adrenal insufficiency were not consistent (Rensen *et al.* 2017).

Immunotherapy

Immune check point inhibitors are used in the treatment of a number of adult and childhood cancers. These agents block the T-cell-mediated inhibitory signalling pathways by modulating immune check point proteins, such as T-lymphocytes antigen-4 (CTLA-4) and programmed cell death receptor-1 (PD-1), to prevent tumour proliferation (Shankar *et al.* 1997). However, the inhibitory action may result in several autoimmune side effects including thyroiditis, adrenalitis and hypophysitis. To date, there is minimal evidence in the long-term endocrine effects of immunotherapy in childhood cancer survivors. Data extrapolated from adults treated with immunotherapy reported a prevalence of primary adrenal dysfunction in 0.3–1% (Joshi *et al.* 2016).

Oncology treatment and autoimmune diseases

An increased prevalence of autoimmune diseases has been observed in childhood cancer survivors. An increased production of antibodies due to immune abnormalities after chemotherapy or immunotherapy, and the increased number of infection during cancer treatment have been hypothesised as the potential pathophysiology. A Scandinavian cross-sectional study of 20,000 adult childhood cancer survivors reported a 1.4 increase risk in hospital contacts for an autoimmune disease over background population. Addison's disease was the second most common condition in terms of hospitalisation (=13.8) and absolute excess risk (=13). Significant increase was reported among survivors of leukaemia, Hodgkin's lymphoma, renal tumours and CNS neoplasms. However, given the high % of CNS tumours in the group, it is possible that some cases of secondary adrenal

insufficiency after treatment with glucocorticoids may be incorrectly recorded as Addison's disease (Holmqvist *et al.* 2016). Childhood-onset autoimmune adrenal disease is extremely rare in cancer survivors, with only one isolated case of primary adrenal insufficiency reported to date, in a 9-year-old child 17 months after busulfan and cyclophosphamide-based conditioning for HSCT (Savas-Erdeve *et al.* 2011).

Patient factors

Time post treatment

A longitudinal study by Laughton *et al.* showed that in survivors of childhood embryonic tumours and medulloblastoma, ACTH deficiency was uncommon in the first 6 months after cranial or craniospinal irradiation exposure, but escalates afterwards with a 4-year cumulative incidence of 38% (Laughton *et al.* 2008). HPAA abnormalities develop over time in childhood cancer survivors post cranial radiation with an increase in incidence and severity with longer time following treatment (Darzy 2009). Progression may be caused by gradual parenchymal cell loss from degenerative vascular changes and mitotic cell death of capillary endothelial cells as a result of radiation damage (Darzy & Shalet 2009). Long-term surveillance with serial testing is important in childhood brain tumour survivors at risk to detect late-onset HPAA dysfunction.

Other factors

Females may be relatively protected from ACTH deficiency in tumours of the hypothalamus and vicinity (Gan *et al.* 2015). The pathophysiology is unclear, but higher total cortisol levels in female patients on oestrogen replacement may be a possible explanation (the proposed mechanism is discussed in the 'Laboratory considerations in cortisol measurements' section). In terms of age at exposure, while younger age at cranial irradiation was associated with increased risk of growth hormone deficiency in childhood cancer survivors, this has not been shown with cortisol deficiency (Shalitin *et al.* 2011).

Assessment of HPAA dysfunction in childhood cancer survivors

Medical history is important although symptoms of HPAA dysfunction may be absent or subtle with fatigue, reduced stamina and poor weight gain, which are generally common in cancer survivors. Therefore, vigilance is

necessary to ensure those at risk are investigated proactively. It is also important to be aware that ACTH deficiency may co-exist with other pituitary hormone deficiencies and the diagnosis may only be unmasked after the supplementation of these hormones, such as when starting thyroxine, which enhances metabolism and growth hormone that normalises 11 β -hydroxysteroid dehydrogenase type 1 overactivity leading to an increase in the conversion of active cortisol to inactive cortisone (Giavoli *et al.* 2004). It is therefore important to assess ACTH function and initiate cortisol replacement before other hormones in patients with potential co-existing ACTH deficiency and central hypothyroidism or growth hormone deficiency to prevent the risk of adrenal crisis.

Surveillance guidelines

Due to the diagnostic challenges in HPAA dysfunction, the timing of the diagnosis has been historically dependent on the referral for endocrine assessment. Therefore, risk stratified surveillance guidelines with evidence-based recommendations on the method, timing and frequency of screening are currently lacking but important to develop for the future. International consensus guidelines on the follow-up of CNS neoplasia and HP dysfunction are under development.

The latest Children's Oncology Group Long-Term Follow-Up Guidelines recommend yearly endocrine evaluation for HPAA dysfunction in survivors if the radiation dose to the HP axis is >30 Gy (Children's Oncology Group 2013). This replaces previous recommendations where patients received >40 Gy are screened by a yearly 08:00h cortisol. However, these guidelines do not specify the definition of an endocrine evaluation, and it is unclear whether an early morning cortisol and/or dynamic tests should be included each time. Reassessment of HPAA status after high dose or prolonged courses of steroids needs to allow for a potentially long recovery time. Repeat assessment is essential even up to a couple of years after the completion of oncology treatment, particularly in those who do not have obvious risk factors for long-term HPAA dysfunction, but required glucocorticoid replacement for suboptimal cortisol response in the acute period.

Biochemical investigations

There are a number of different biochemical tests available to assess HPAA function, and the most appropriate method for each individual relies on clinical judgement. A clear understanding of the principles and limitations

of the tests are essential to avoid diagnostic pitfalls. Table 3 summaries the pros and cons of the common investigations used to assess HPAA function in childhood cancer survivors in clinical practice and research.

Baseline (unstimulated) ACTH and cortisol levels

Early morning (08:00–09:00h) unstimulated cortisol and ACTH levels are often used as a routine screening test for central or secondary adrenal abnormalities. A cortisol level of >300nmol/L has previously been reported to exclude significant ACTH deficiency in patients post radiotherapy (Darzy 2009), but local variations in laboratory assays must be considered. Only an elevated plasma ACTH with an extremely low cortisol level is useful in the context of primary adrenal insufficiency as low ACTH levels may not be measurable and are hence not diagnostic of central deficiency.

There are a number of drawbacks in using early morning ACTH and cortisol levels. Considerable overlap exists between normal individuals and those with adrenal insufficiency (Ranke & Mullis 2011). Circadian rhythm is not present in the very young under 3 months of age or seriously ill patients. Unstimulated cortisol levels do not necessarily reflect the individuals' response under stress. Finally, ACTH is unstable in blood with a short (<10-min) half-life and samples must be handled appropriately. Therefore, there should be a low threshold in proceeding to dynamic tests in at-risk patients.

Insulin tolerance test

The ITT allows simultaneous assessment of ACTH and growth hormone function. HPAA assessment using the ITT is based on the principle that hypoglycaemia causes neuroglycopenia, which activates corticotropin-releasing hormone (CRH) secretion from the hypothalamus, enhances ACTH release from the pituitary gland, and in turn, cortisol production. It is considered the gold standard for HPAA assessment, particularly after cranial irradiation, which affects the hypothalamus more than the pituitary gland. However, the ITT raises safety concerns in patients with poor counter regulatory responses to hypoglycaemia, and the test is contraindicated in patients with cardiac diseases and epilepsy. The test must only be carried out in specialised centres by experienced personnel.

ACTH (Synacthen) stimulation test: standard and low dose

The ACTH stimulation test primarily assesses adrenal cortex function. However, in view of the risk of the ITT,

Table 3 Summary of investigations for HPAA function.

Test	Pro	Cons
Early morning cortisol	<ul style="list-style-type: none"> • Easy • Safe 	<ul style="list-style-type: none"> • Overlap between normal and abnormal results • Does not reflect ability to mount response at stress • Lack of circadian rhythm in the very young and sick
Insulin tolerance test	<ul style="list-style-type: none"> • Gold standard post cranial irradiation • Enable simultaneous assessment of pituitary ACTH and GH reserve 	<ul style="list-style-type: none"> • Relatively invasive and labour intensive • Hypoglycaemia risk (contraindicated in patients with seizures and cardiac disease)
ACTH stimulation test (low and standard dose)	<ul style="list-style-type: none"> • Low cost • Relatively safe 	<ul style="list-style-type: none"> • Controversies with dosage (standard vs low dose) <ul style="list-style-type: none"> – Poor sensitivity (standard dose) – Poor specificity (low dose) • Anaphylaxis risk (low) • Lose dose difficult to titrate accuracy
Corticotropin-releasing hormone test	<ul style="list-style-type: none"> • Distinguish hypothalamic to pituitary abnormalities 	<ul style="list-style-type: none"> • ACTH unstable
Cortisol profiling	<ul style="list-style-type: none"> • Shows physiological circadian rhythm of cortisol release 	<ul style="list-style-type: none"> • Labour intensive • Does not reflect ability to mount response at stress • Lack of circadian rhythm in the very young and sick

it is often used as an alternative in the investigation of secondary adrenal insufficiency, assuming that chronic ACTH deficiency results in atrophy of the adrenal cortex and failure to respond to exogenous corticotrophin. The optimal dose for this purpose is debatable and some advocate the LDST. A retrospective review of childhood cancer survivors who underwent HPAA assessments in childhood cancer survivors reported normal function in 89% by the standard dose Synacthen stimulation test (SSST) but only 65% by LDST (Patterson *et al.* 2009). A systematic review and meta-analysis showed that the LDST (0.5–1 µg/m², maximum 1 µg) has a higher sensitivity (86% vs 61%), but a lower specificity (88% vs 99%) than the SSST (250 µg/1.73 m², 250 µg max). However, comparisons of the two tests are limited due to the lack of standardisation of assays and protocols with regards to timing, frequency and dose (Ng *et al.* 2016). It can be challenging to titrate the precise dosage for patients of very small size and the test does not distinguish between hypothalamic and pituitary pathologies.

Although the ACTH stimulation test may appear to be a safer and easier option than the ITT for HPAA assessment, false negatives from previous research in childhood cancer survivors raised concerns of cases missed. Schmegelow *et al.* who evaluated the HPAA with both an ITT and an ACTH test 15 years after treatment for brain tumours showed 30% of the patients passed the ACTH test, but failed the ITT while no patients passed the ITT and failed the ACTH stimulation test (Schmegelow

et al. 2003). Of note, results of the ACTH stimulation test may be normal in the acute period in patients developing central hypocortisolaemia.

CRH test

The CRH test assesses the ability of the pituitary gland to secrete ACTH for cortisol production. Patients with pituitary dysfunction show impaired secretion of ACTH and cortisol while those with hypothalamic abnormalities will have an exaggerated and prolonged ACTH response with suboptimal peak cortisol levels. In clinical practice, this test is usually reserved for patients when other tests are contraindicated.

Cortisol profiling

Twenty-four-hour ACTH and cortisol frequent venous sampling demonstrates the physiological hormone secretion of the HPAA. However, this method is labour intensive and does not assess the individuals' ability to mount a normal response under stress. It is usually reserved for research studies or in some centres dose monitoring in patients on steroid replacement.

Laboratory considerations in cortisol measurements

Regardless of the method of assessment, it is important to appreciate that cortisol measurements are influenced significantly by the laboratory assay used.

Older immunoassays over-estimated results due to interferences from cross-reactivity with corticosterone. New-generation assays have lower acceptable cortisol peak levels as normal. For example, while a peak cortisol level of over 500–550 nmol/L was historically considered as normal for a SSST, some of the newer cortisol assays produce results closely aligned to mass spectroscopy method with a cut-off of approximately 420 nmol/L as an adequate response (Hawley *et al.* 2016).

In addition, other factors may interfere with cortisol measurements. Oral oestrogen, in particular, increases cortisol-binding globulin and hence the total cortisol levels. Therefore, while free cortisol levels are not affected, a higher reference range is needed when interpreting the results reporting total cortisol level (El-Farhan *et al.* 2013). However, the same problem has not been observed in patients on transdermal oestrogen replacement (Qureshi *et al.* 2007). This information is important when assessing HPAA function in female childhood cancer survivors as gonadal failure is common and patients may be on sex hormone replacement therapy.

Relationship between HPAA function and wider aspects of health

There has been increasing research interest in the relationships between HPAA function and wider aspects of health such as chronic physical and psychological stress, neuro-cognition and chronic fatigue syndrome in childhood cancer survivors. Pilot data suggested that the metabolic syndrome in childhood cancer survivors may be associated with alterations in the HPAA suggesting chronic stress (Yeap *et al.* 2005). Survivors of childhood leukaemia treated without cranial irradiation have demonstrated increased morning cortisol levels with intact endocrine and cardiovascular responses to social stress in the short term (Gordijn *et al.* 2012, 2013). However, a potential impact of adrenal insufficiency on neurocognitive outcomes has been reported in leukaemia survivors (Cheung *et al.* 2017). Symptoms that characterise chronic fatigue syndrome and autonomic dysfunction have been described in childhood cancer survivors, which have overlapping features with HPAA dysfunction. Zeller *et al.* reported reduced levels of plasma ACTH and raised urine noradrenaline in survivors of childhood cancer with chronic fatigue suggesting slight inhibition of the HPAA and enhanced sympathetic nervous system activity, which is similar to non-cancer survivors with chronic fatigue syndrome (Zeller *et al.* 2014). Long-term alterations in the HPAA and its associated physical, psychological and

social consequences, in childhood cancer survivors still require evaluation in larger prospective patient cohorts with longer follow-up time to investigate potential impact on health and quality of life.

Future directions

Continued systematic longitudinal data collection in all aspects of late effects in childhood cancer at national and international levels is needed to enable oncology treatment related abnormalities to be reported in line with evolving treatment protocols and new modalities. In addition to providing up-to-date information on the prevalence of HPAA abnormalities, outcomes will also highlight risk factors to allow targeted screening in vulnerable patients. There is ongoing debate on the most appropriate methods of screening and confirmatory test to diagnose HPAA dysfunction in childhood cancer survivors. International consensus is needed to standardise the methods and rationalise the frequency of screening to ensure timely and appropriate investigations.

Summary and conclusions

In summary, HPAA dysfunction is relatively less common compared with other pituitary hormone deficiencies in childhood cancer survivors, but highly significant when it occurs. The incidence and prevalence of HPAA dysfunction reported in the literature are variable due to heterogeneity in patients' characteristics, primary diagnoses and treatment protocols, as well as surveillance methods used to assess HPAA function.

The key clinical messages from this review are

- Clinicians managing childhood cancer survivors must be well informed of their diagnosis and treatment background to appreciate the risk of long-term morbidity for individual patients and tailor appropriate surveillance.
- ACTH deficiency may develop many years after the completion of oncological treatment alongside multiple pituitary hormone deficiencies due to factors such as low-grade tumour progression and evolution of cranial irradiation effects with time.
- In general, childhood cancer survivors most at risk of ACTH deficiency are
 - o those who had tumours located and/or had surgery performed near the HP region,
 - o those who received accumulative HP radiotherapy dose of over 30 Gy.

- As clinical symptoms are often minimal, the diagnosis of HPAA dysfunction may be delayed without routine surveillance and formal assessment.
- It is important to re-evaluate HP function in patients on glucocorticoid replacement, with potential secondary adrenal insufficiency after high-dose or longer term glucocorticoid treatment to ensure treatment is continued or discontinued appropriately.

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