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Paediatric Update

Growth and endocrine function after chemotherapy and radiotherapy in childhood

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1. Introduction

85% of childhood cancer survivors, particularly those treated youngest, most intensively or for central nervous system (CNS) tumours, face cognitive, neuropsychological and endocrine impairment. Future challenges include the prevention of premature mortality from treatment-induced second tumours, cardiac, pulmonary and renal toxicity, and morbidity from hypopituitarism, obesity and their metabolic consequences. Improving quality of life (QoL) by early hormone replacement, preservation of fertility and neuropsychological rehabilitation will enable these young people to achieve employment, independence and successful peer relationships.

2. The changing therapeutic baseline

Cranial and total body irradiation (TBI), both responsible for late neurocognitive and endocrine toxicity [1–3], are increasingly being substituted by more aggressive chemotherapy and/or the reduction, hyperfractionation or more focal (stereotactic) application of the cranial irradiation dose. However, it is unclear whether these strategies compromise cure or the quality of survival. Chemotherapy may cause neural and endocrine toxicity [1], whilst the pre-existing disease and its perioperative course must also contribute, particularly where the CNS tumour site is 'central' [4–6], (i.e. close to the thalamic, suprasellar, and hypothalamo-pituitary areas (HPA)), rather than more lateral or inferior. The few available longitudinal studies suggest that irradiation compounds, an already pre-existing neurosecretory dysfunction and that chemotherapy is additively toxic, to both the CNS [7] and peripheral target glands [8,9]. Furthermore, endocrinopathies, skeletal irradiation, chemotherapy and glucocorticoids, malnutrition and prolonged ill-health all independently influence sexual maturation and bone mineral accretion, thereby confounding data on infertility or osteopenia in survivors [10]. The picture has also been confused by discrepancies between 24-h physiological and pharmacological hormone secretion in longitudinal [7,11] and cross-sectional survivor studies [12,13] of cranial irradiation, the long evolutionary time course, the largely retrospective, cross-sectional studies and the changing multimodal and individually tailored therapy baseline.

Although final height and fertility are important endocrine endpoints, current data often relate to already outdated treatment regimens, whilst better surgical, supportive and rehabilitative opportunities including new assisted reproduction techniques and better school awareness of individual needs will surely alter outcome, hopefully for the better, for those undergoing treatment today. Before the balance between cure and late morbidity can be truly evaluated, the toxicity of new cancer treatments must be critically appraised over many years.

3. Radiobiology and late neuro-endocrine toxicity

In general, the radiosensitivity of a tissue is directly proportional to its mitotic activity and inversely proportional to its degree of differentiation [14]. All organs are damaged by irradiation, but the late effects on specialised, slowly- or non-proliferating cell populations (such as the brain) are manifest only with time. Fractionation of the dose generally improves the therapeutic margin, but there is evidence to suggest the gonads are an exception to this rule [14,15]. Other long-term consequences include life-shortening mutagenicity and carcinogenesis [14,16].

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With conventional external beam radiotherapy, late neuroendocrine effects depend upon the volume of the brain irradiated, the fraction size and interfraction interval, the age of the child, the total dose delivered and the time elapsed since injury [6,17]. The irradiation field for most infratentorial childhood brain tumours is demarcated by the pituitary margins and the pituitary dose is at least 40–45 Gy. The highest hypothalamo-pituitary doses (up to 70 Gy) occur after treatment for nasopharyngeal tumours, with consequent multiple pituitary deficits [18]. Yttrium-90 implants and the newer stereotactic irradiation techniques, although more focused, currently have limited application in childhood cancer.

3.1. Chemotherapy, radiation and toxicity

Additive effects from combined drugs and radiation may cause cumulative toxicity in late-responding tissues, without time for regeneration between the two treatment modalities. Toxicity to the thyroid [8], gonad [9] and skeleton [19], as well as to central pituitary hormone secretion [7], is greater when adjuvant chemotherapy and irradiation are combined. Thus, using chemotherapy to delay, but not necessarily avoid, potentially curative cranial irradiation in the youngest children [2,3] may cause additive injury that is evident only in the longer term.

4. Consequences of cranial irradiation

4.1. Panhypopituitarism

After surgery for pituitary tumours, the few (37/165 in one series) adults with more than one intact pituitary hormone suffer an evolving 'postirradiation' (20–45 Gy) endocrine deficit which is dose- and fractionation-dependent and hierarchical in nature [6,17] (Fig. 1a). However, delayed tumour- or surgery-induced neuronal injury may also play a part. Experimental pituitary irradiation in rats [20] causes the characteristic growth hormone (GH) deficit seen in humans [6], but not the ACTH and gonadotropin deficiency. Furthermore, the relative radioresistance of TSH and prolactin secretion noted in the human subjects [6] is absent in rats, these hormones and GH being affected early [20]—perhaps a reflection of their common developmental origin [21]. Postirradiation pituitary deficiencies are also noted in children after high doses (>50 Gy) for orbital and middle ear tumours [22] and after lower cranial doses for brain tumours (30–50 Gy) or leukaemia (18–24 Gy)[23], but the high prevalence of deficiencies other than GH noted in the adult pituitary studies[6] have not been confirmed in childhood survivors of posterior fossa or laterally placed tumours (only 2–6%) [5,7–9,24,25], despite similar pituitary doses and 10 years of follow-up. GH deficiency is the earliest and often the only abnormality and the deficit is usually permanent [24,25] (Fig. 1b).

Given the clear-cut time- and dose-dependency, pituitary deficiencies are likely to be multiple and to manifest quickly and most completely in the youngest children receiving the highest irradiation doses or where tumours are close to the HPA, i.e. 'central' [6,18]. By contrast, they may be single, evolve more slowly or be qualitative rather than quantitative in nature after irradiation to more laterally-sited tumours [7,25] or after the lower cranial doses used in leukaemia prophylaxis [11,23,26] and total body irradiation (TBI) [12,27,28], particularly if the fraction size is also reduced (Table 1). This may well result in a cohort of survivors who need hormone replacement therapy as adults rather than as children [29].

4.1.1. Nature and site of the neuro-endocrine defect

Whether the postirradiation endocrinopathy is neural or vascular, hypothalamic or pituitary, is still hotly debated. The few available studies do not suggest that either hypothalamic [30] or hypophyseal-portal blood flow [31] are compromised. The hypothalamus or its portal connections are perceived to be more radio-sensitive than the pituitary. Evidence cited includes hyperprolactinaemia attributed to disrupted hypothalamic inhibitory dopaminergic tone [18,20], after >50Gy [20], for nasopharyngeal or pituitary tumours. However, hyperprolactinaemia is not seen after treatment for extrasellar tumours in childhood [18,24,25] nor has diabetes insipidus, a typical hypothalamic disorder, been reported [18]. Selective damage to hypothalamic control centres is suggested by discordant suppression of insulin- mediated and spontaneous GH release in irradiated rhesus monkeys [32], children with leukaemia [12,33] and brain tumours [7] and paradoxically preserved GH responses to other centrally-acting agents or hypothalamic releasing factors [34,35]. Since GH secretion [7,13,24] and pituitary GHRH responses [24,34,35] decline with time, direct pituitary damage is a possibility.

Spontaneous GH secretory profiles *before* low (10 Gy) [12] or high (30–50 Gy) [7] cranial irradiation doses already reveal disturbed GH pulsatility, with suppressed insulin-induced and paradoxically-preserved physiological GH peaks. We proposed [7] that the disease (cerebellar tumour) and/or its surgery, somehow disrupt afferent or efferent GH chemoreceptor responses to hypoglycaemia and suppress hypothalamic somatostatin secretory tone, important in regulating GH pulsatility. Superimposing cranial irradiation also suppresses physiological GH peak generation, suggesting eventual hypothalamic GH-releasing factor (GHRH) deficiency [7], and possible consequent dysfunction or atrophy of the pituitary somatotroph [24,35]. Chemotherapy plays an important contributory part in this evolving neural dysregulation at the HPA [7] (Fig. 2).

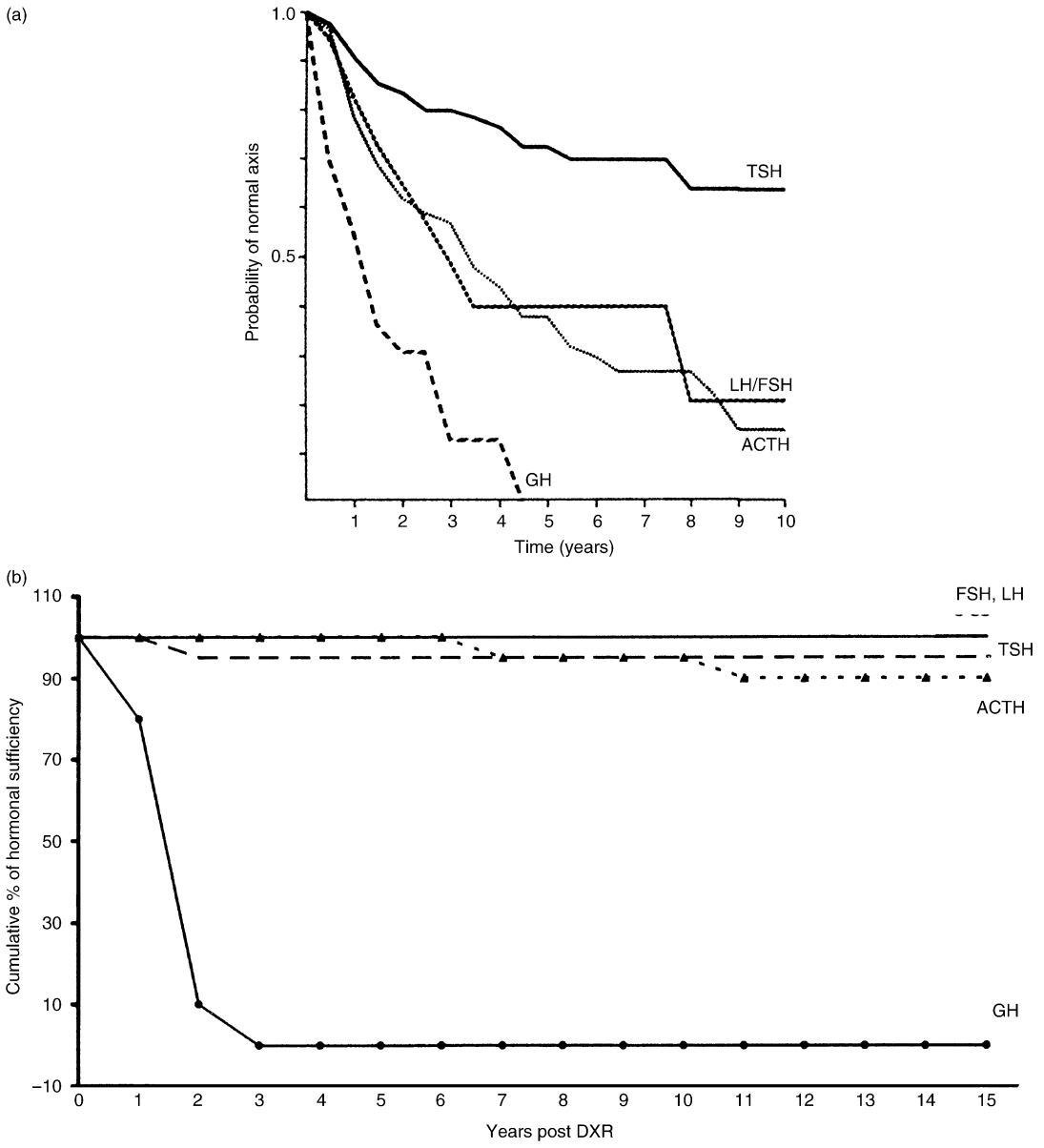

Fig. 1. (a) 10-year life-table analysis, in 37 of 165 adults with intrasellar or anatomically adjacent tumours, and normal postoperative hypothalamo–pituitary function, indicating the likelihood of an evolving endocrinopathy after 37.5–42.5 Gy pituitary irradiation in 15 fractions over 20–22 days (redrawn from Ref. [8]). GH is most sensitive, all adults being GH deficient within 5 years, whilst ACTH and Gonadotrophins (LH $ FSH) are increasingly affected over time (80% at 10 years). TSH is most resistant. (b) 10-year probability of an evolving endocrinopathy, occurring after a median estimated hypothalamo-pituitary irradiation dose (DXR) of at least 40 Gy in 1.8 Gy fractions, in 20 young adult survivors of resected posterior fossa brain tumours tested twice—at the onset of growth failure and at completion of growth—who were otherwise asymptomatic (redrawn from Ref. [28]). GH deficiency was present in all patients tested at first assessment and was permanent. ACTH (10%) and TSH (5%) deficiencies were comparatively rare and there was no case of Gonadotrophin deficiency or hyperprolactinaemia over the duration of follow-up. Note the diminution in oscillatory activity with time and intensity of therapy, suggesting compounding central hypothalamic disturbance by treatment modalities, evolving over time.

The distinction between hypothalamic and pituitary dysfunction has therapeutic relevance. Hypothalamic gonadotrophin- and growth hormone-releasing factors restore fertility [36] and growth [37], respectively, but only if the pituitary is intact. Because the response to GHRH also depends on hypothalamic somatostatin secretion which is disturbed by cranial irradiation [7,12], GH-releasing factor therapy is less effective than recombinant human GH (*r-h*GH) in enhancing growth [37]. If the aetiology and site of the damage are accurately determined, protective strategies can be attempted before irradiation commences [38].

4.2. Growth failure and growth hormone deficiency

Growth failure, disturbed physiological GH secretion and/or attenuated stimulated peak GH responses affect 60–100% of children within 2–5 years of fractionated

Table 1
Likely endocrine deficit according to cranial irradiation dose (brain tumours distant from pituitary area)

Dose (Gy)	Endocrinopathy
>55–70	Hyperprolactinaemia, panhypopituitarism
30–55	GH insufficiency, evolving endocrinopathy
18–24	Neurosecretory disturbance, pubertal GH insuffiency, early puberty, adult GHD
10–15 Gy	Neurosecretory disturbance, adult GHD

GHD, growth hormone deficiency.

(<2 Gy) cranial irradiation doses of >30 Gy [4,5,7]. The speed of onset is dose-dependent [17], but there is unlikely to be a lowest 'safe' dose. The few studies of physiological 24-h GH secretion before and after TBI (10 Gy) [12], cranial irradiation (24 Gy) for leukaemia [39] or brain tumours distant from the HPA (>30 Gy) [7] suggest a steadily evolving picture of neurosecretory disturbance with time and irradiation dose intensity [7,12,39], which is eventually severe and permanent [24,29,35]. Abnormalities in GH pulsatility after 10 Gy of slow dose-rate TBI [12] or fractionated (2 Gy) cranial doses of 18 Gy [39] and 24 Gy [40] are particularly evident in puberty [26,40]. More favourable reports [39] have assessed mean or peak GH secretion only and may miss the early qualitative, subtle disturbances in GH pulsatility and failure to augment pubertal GH secretion adequately [26,40].

4.2.1. Diagnosing GH deficiency

Discrepancies between growth velocities, stimulated GH responses and 24-h endogenous GH secretion [11,12,33] complicate the diagnosis of GH deficiency in survivors of acute leukaemia. By contrast, these discrepancies are rare after the higher cranial irradiation doses used to treat brain tumours, except when studied within 2 years of diagnosis [7], presumably due both to the greater speed with which GH deficiency develops and the degree of the deficiency.

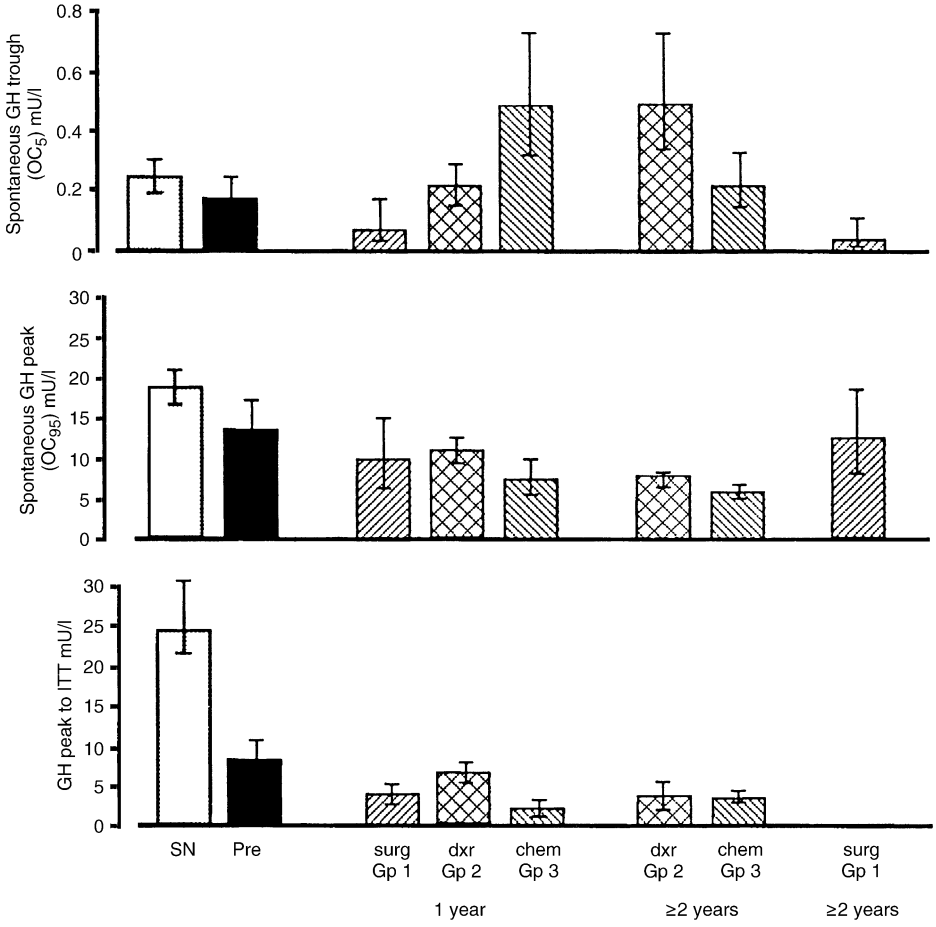

Fig. 2. Relationship of spontaneous GH troughs (OC_5, upper panel), spontaneous GH peaks (0C 95, middle panel) and stimulated peak GH responses to hypoglycaemia (ITT, lower panel), with increasing therapeutic intensity and time in short normal (SN) controls, and children with brain tumours before (pre) radiotherapy and at 1 and 2–5 years after neurosurgery alone (surg, Gp1), or with additional >30 Gy cranial irradiation (dxr, Gp 2), and >30 Gy dxr with adjuvant chemotherapy (chem, Gp 3) (redrawn from Ref. [3]) Note the wide variation in trough secretion across groups compared with controls, and the marked early discrepancy between spontaneous (preserved) and stimulated (attenuated) peaks, even in children treated with surgery only (Gp 1). This discrepancy becomes concordant with time and intensity of therapy as spontaneous GH secretion fails (redrawn from Ref. [3]).

Serum insulin-like growth factor-1 (IGF-1) and its binding protein, (IGF-BP3) are also unreliable estimates of 24-h [24,35] or stimulated [35,41] GH secretion in cranially irradiated children. Possible reasons include disrupted hypothalamic feedback [35], nutritional influences early in the disease [41], pubertal hormonal changes and increased IGF-BP3 protease activity in malignancy. However, as the severity of GH deficiency evolves with time, the accuracy of the tests improves to 83 and 71% for IGF-1 and IGF-BP3, respectively [24] (Fig. 3).

The lack of a 'gold standard' for assessing GH secretory status makes it imperative that all slowly growing children have a full endocrinological assessment. Adult survivors of low cranial irradiation doses are at real risk of adult GH deficiency [29] with its attendant implications for bone mineralisation, body composition, lipid profile and quality of life.

4.2.2. The influence of chemotherapy on growth

4.2.2.1. Leukaemia. Growth retardation during treatment for acute leukaemia is partially counteracted by 'catch-up' after cessation of 'maintenance' chemotherapy. However, depending on the intensity of chemotherapy, significant height loss can be detected in 40–70% [42,43] of patients at 6-year follow-up. Chemotherapy also aggravates the growth failure of children with brain tumours given craniospinal irradiation [19] and deficient short-term growth has also been described in children given only chemotherapy, without cranial irradiation [44,45] or TBI [46]. However, irradiation probably causes the long-term deceleration which is not so evident in the chemotherapy-only group [44].

Studies *in vitro* [47] and *in vivo* [45] have shown that chemotherapeutic agents suppress human osteoblast proliferation and enhance osteoclast activity. Glucocorticoids modify these actions [48] and have their own negative effects on growth and bone mineralisation. The disease induces a low bone turnover and GH-resistant state aggravated by chemotherapy. Disease control, weight gain and glucocorticoid withdrawal increase bone and soft tissue turnover and growth velocity. This effect is reduced by methotrexate [45], whilst alkylating agents and anitimetabolites also cross the disrupted blood–brain barrier and perturb central GH secretion [7].

Not all patients with leukaemia require growth-directed investigation or therapy. Nevertheless, despite temporary 'catch-up', 90% of 115 children aged <12 years at irradiation (24 Gy) suffered mean adult height deficits of 1 (5 cm) (67%) or 2 (10 cm) standard deviations (S.D.) (33%) from pretreatment scores, spinal irradiation aggravating the problem [49]. In those treated before the age of 7 years, attenuated pubertal growth is evident [44] and accords with failure to augment pubertal GH secretion [26,40] as described in the previous section. Asymmetric body proportions (longer legs) of adult survivors [50] pretreated with cranial, but not spinal, irradiation is also suggestive of compromised pubertal, spinal growth from undiagnosed pubertal GH insufficiency. Similar disproportion is evident in a cohort of brain tumour survivors, even those not given spinal irradiation [5] (Fig. 4) stressing the importance of specialist endocrine input, both before and during puberty, before the 'window of opportunity' for treatment is lost.

4.2.3. The influence of spinal irradiation on growth

4.2.3.1. Hodgkin's disease. Spinal growth impairment and skeletal disproportion were first described after 18 fractionated doses of 44 Gy to the midplane in both mantle and 'inverted Y' fields [51]. Estimated vertebral scatter ranged from 40 to 100% despite shielding. The height deficit was worse in children irradiated under the age of 6 years or during puberty [51].

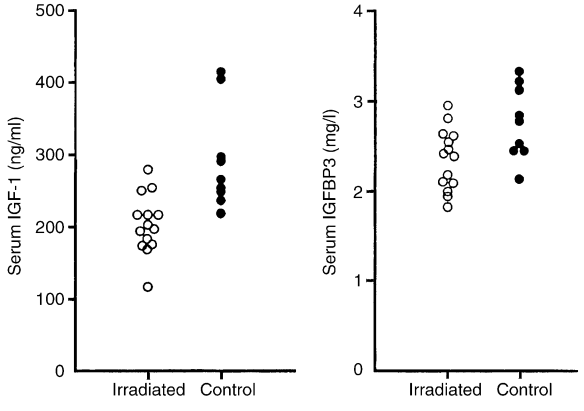

Fig. 3. Serum IGF-1 and IGF-BP3 levels in long-term (13 years) adult survivors of cranial irradiation for posterior fossa tumours (open circles) and controls (closed circles) (redrawn from Ref. [13]). IGF-1, insulin growth factor-1; IGF-BP3, insulin growth factor-binding protein 3.

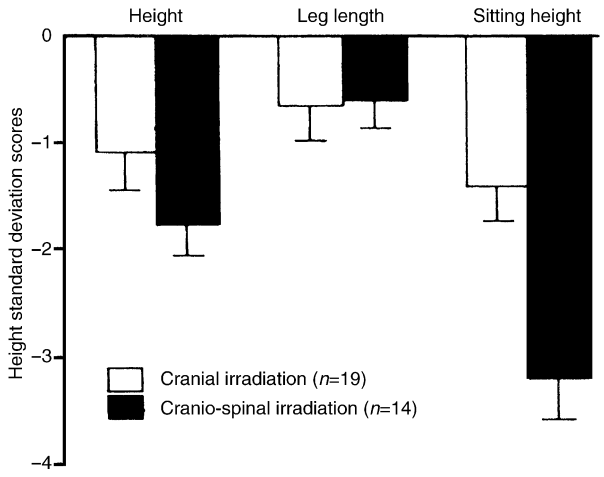

Fig. 4. Adult height without endocrine therapy of 33 patients irradiated in childhood for brain tumours (redrawn from Ref. [7]). All patients are short, but the greatest deficit is seen in the spine, even in those not receiving spinal irradiation, although less severe, suggesting a subtle GH disturbance affecting pubertal (and hence) spinal growth.

4.2.3.2. Brain tumours. Craniospinal irradiation (27–35 Gy in 22–27 days) impairs spinal growth [10,52] (Fig. 4). The younger the child the greater the deficit which is estimated at 9 cm if irradiation is administered at 1 year, 7 cm at 5 years and 5.5 cm at 10 years [52]. Spinal growth is a major component of the pubertal growth spurt so the disproportionate deficit, compounded by pubertal GH deficiency, may only then become apparent, at a time when growth promotion is limited. Hyperfractionation may decrease the deleterious effects [53] if the overall treatment time is simultaneously accelerated.

4.2.3.3. Leukaemia. Almost 50% of those receiving craniospinal irradiation (24 Gy) suffered height loss of >2 S.D. from pretreatment values, as compared with 32% of their peers receiving only cranial irradiation (24 Gy) and intrathecal methotrexate. Furthermore, no 'catch-up' growth was observed in the craniospinal group, presumably due to the absence of a significant spinal pubertal spurt [49]. Chemotherapy and steroids are contributory [45,48,49].

4.2.3.4. Total body irradiation. Both single (7.5–10 Gy) and fractionated (12–15.75 Gy) TBI regimens cause progressive growth failure [54–56], 33% of patients being >2 S.D. below the mean at 5 years [56]. This is partly due to GH deficiency, which increases with time and irradiation dose (42 and 87% of those transplanted in first and second remission, respectively), and is not observed after chemotherapy alone [55], but is also due to growth plate and bony matrix damage [51]. Disruption of bone matrix integrity must account for the poor growth response to *r-h*GH [56], the lack of correlation between GH secretion and height loss [57] or growth rate [46] and the accrual of further height deficits despite *r-h*GH therapy [58]. Other endocrinopathies, steroid and cytotoxic therapy [47–48] and graft versus host disease may also be involved. Patients should be warned that, at best, pretreatment centile positions can only be maintained by *r-h*GH therapy, and that at worst, additional pubertal and thus adult height deficits are likely (Fig. 5).

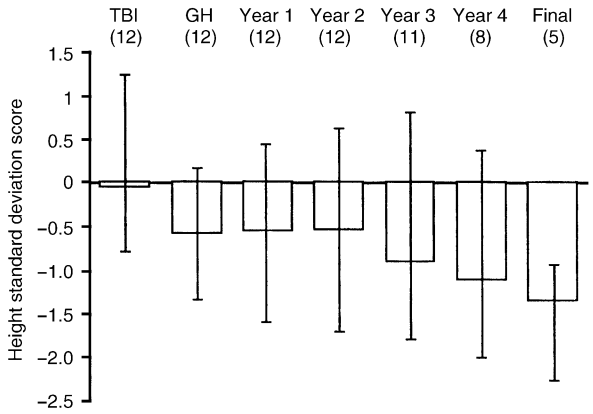

Fig. 5. Stature (expressed as height standard deviation scores (SDS)) of 12 leukaemic children at our centre who were prepubertal at the time of TBI (TBI), followed longitudinally to adult height from the time of growth hormone replacement (GH) for confirmed GH deficiency. The numbers of subjects are shown in parentheses). Note that institution of GH therapy initially only maintains the height position without 'catch-up growth', and subsequently fails to prevent an ongoing pubertal deficit to adult height.

4.3. Precocious puberty

Precocious (early) puberty is a recognised presentation of optic, hypothalamic and other 'central' tumours, but has also been detected after treatment for more laterally- or inferiorly-placed tumours [5,59]. Possible coexistent gonadotoxicity induced by chemotherapy [60,61] or spinal irradiation [9] confounds the true prevalence. Gonadotrophin deficiency arresting pubertal development is also possible [9], although more likely after high dose irradiation of pituitary or closely-located tumours [17]. For a more detailed discussion of the effects on fertility and progeny following the diagnosis of childhood cancer see an earlier update by Thomson and colleagues published in the previous issue of the EJC [62].

Early puberty, directly related to the age at irradiation [59], occurs particularly in girls, whose hypothalamic gonadotrophin pulse generator is known to be more sensitive, but also in boys, and is more evident after lower (24 or 18 Gy), rather than higher, cranial irradiation doses. This finding has become more evident since spinal irradiation was omitted from neuraxial prophylaxis [63] (Fig. 6). The increased prevalence of early puberty in females treated with 18 Gy rather than 24 Gy cranial irradiation [63], suggests that damage to higher puberty-inhibitory centres may occur after low cranial irradiation doses, whilst higher doses may ablate hypothalamic GnRH or pituitary gonadotrophin release; the absence of this phenomenon after lower (7.5–15 Gy) TBI doses is explained by its severe gonadotoxicity [64]. Cranially-irradiated female leukaemia survivors are also at risk of obesity [65], raising the possibility that neuroregulatory changes in leptin secretion may contribute to the early puberty [66].

5. Thyroid dysfunction

Radiation damage to the thyroid gland causes hypothyroidism, usually compensated for by increased TSH production, and thyroid tumours. Hypothyroidism is dose- and time-dependent and has been well documented after fractionated doses to the neck in excess of 25 Gy [67]. The suggestion that its incidence is greater in the youngest patients has not been confirmed [68].

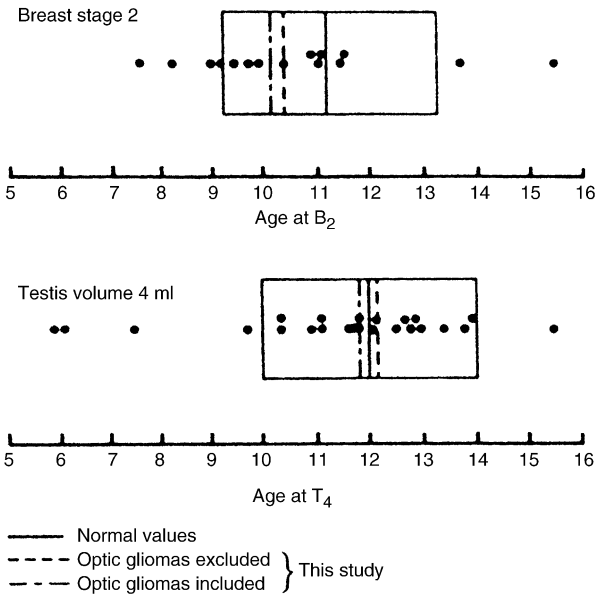

Fig. 6. Age at pubertal onset of 15 girls and 24 boys receiving 10–56 Gy fractionated cranial irradiation for brain tumours distant from the hypothalamo-pituitary axis. The solid line boxes represent the mean±2 S.D. for normal children; the broken lines represent the study population medians with optic gliomas excluded (....) or included (- - - - -) (redrawn from Ref. [7]).

5.1. Hodgkin disease

In those under 16 years, the prevalence of hypothyroidism within 2 years of 36–44 Gy mantle irradiation (1.5–2 Gy fractions) vary between 37 and 88% [68,69], with 25–53% 'compensated' and 0–58% 'overt'. The use of posterior spinal and laryngeal blocks at 30 and 20 Gy, respectively, did not reduce the overall incidence of hypothyroidism (57%) although it was overt in fewer cases (5%) at a median follow-up of 65 months [70].

Transient hyperthyroidism has been reported after adjuvant mechlorethamine, vincristine, procarbazine and pednisone (MOPP) chemotherapy [68] treated without neck irradiation, and just one report documents primary thyroid dysfunction in 24 of 54 adults with advanced Hodgkin's disease who received chemotherapy but not radiotherapy [71].

5.2. Craniospinal and total body irradiation

Compensated or, less commonly, frank hypothyroidism occurred in 30–40% of children with brain tumours treated with cranio-spinal (30–35 Gy) irradiation, but not chemotherapy, most within 4 years of treatment. Chemotherapy increased this risk [8,72]. A similar proportion developed hypothyroidism, compensated at first and progressing to overt hypothyroidism 5–10 years later, after TBI [54]. After 7.5–10 Gy single fraction TBI, 28 and 13% developed compensated and overt hypothyroidism, respectively. After 12–15.75 Gy fractionated TBI, these figures were 12 and 3%, respectively, although the overtly hypothyroid group were followed for only half the number of years [54,73]. These figures have proved overestimates so far as the long-term is concerned, since recovery occurred in 33% at a median of 60 months and no overt cases of hypothyroidism developed [74].

Elevations in TSH have been attributed to primary thyroid gland damage. Because of the carcinogenic potential of prolonged stimulation in the irradiated gland, annual thyroid palpation (with repeated ultrasound examinations and needle biopsy and thyroidectomy as necessary), and thyroid function tests (with thyroxine replacement if TSH is persistently elevated), are often recommended. However, documented recovery after mantle [68] and spinal irradiation [72] and after TBI [74] raises the possibility that elevations in TSH may be evidence of hypothalamic irradiation damage, disturbing the normal day-to-night TSH variation by obliterating the nocturnal TSH surge [35].

Whilst chemotherapy is apparently additive to the effects of irradiation [8,72], the independent role of the drugs used is probably slight, since thyroid dysfunction was not observed in a large series of 105 children transplanted for thalassaemia and in only 1 of 50 transplanted for aplastic anaemia with 'conditioning' chemotherapy, without TBI [73].

6. Adrenal function

After estimated HPA irradiation doses up to 50–55 Gy given to treat laterally- or inferiorly-placed brain tumours, symptomatic ACTH deficiency has not been reported. 2–13 years after HPA doses far in excess of 50 Gy to adults with nasopharyngeal tumours, an 18–35% dose-related prevalence of asymptomatic, subnormal cortisol response to metyrapone was reported. By contrast, pituitary responses to hypothalamic corticotropin-releasing factor were normal [18].

In a series of 20 cranially-irradiated childhood survivors of posterior fossa tumours, 10 years after estimated pituitary doses of 40–45 Gy at our institution, all but 2 demonstrated adequate (>500 nmol/l) cortisol responses to hypoglycaemia despite persistently suboptimal growth hormone responses [25] (Fig. 1b). The 2 exceptional patients were asymptomatic with normal responses to low-dose ACTH stimulation; in 1 of them, late onset 21-hydroxylase deficiency was diagnosed. This experience contrasts with the high (80%) prevalence of ACTH insufficiency observed in adults [6], suggesting earlier surgery- or tumour-related contributions to the latter. 24-h physiological secretion profiles in children with leukaemia who had received 18 or 24 Gy cranial irradiation 3.5–10 years previously showed no disruption in the amount or pattern of ACTH and cortisol secretion compared with normal controls [75].

Clinical signs of cortisol deficiency may be vague and the diagnosis missed by conventional tests such as insulin-induced hypoglycaemia [76] or standard (250 μg) ACTH (synacthen) stimulation [77], which lack sensitivity due to their pharmacological nature. Low doses of ACTH (500 ng/1.73 m^2) have been proposed as a more physiological test of adrenal reserve [77]. The 24% prevalence of subnormal adrenal responses to metyrapone after TBI [54] suggest that subclinical adrenal damage may develop as time passes.

7. Impaired bone mineralisation

Osteoporosis has been blamed on the adult GH deficiency syndrome [29], but skeletal changes observed in cancer survivors may be also be attributable to other hormonal (sex steroid) deficiencies. Skeletal irradiation [51], corticosteroids and antineoplastic agents [45,47,48] may also impair mineralisation directly or indirectly by inducing renal tubulopathies. Disease (e.g. leukaemia), prolonged bed rest and changes in Vitamin D metabolism may also influence bone mineral density. Concern that a lower peak bone mass in adolescence will cause osteoporosis later, in adult life, is therefore valid. However, the interpretation of surrogate markers of bone mineral density (BMD), such as dual energy X-ray adsorptiometry (DEXA) measurements at the lumbar spine, needs to be undertaken with care. Sex- and age-standardised reference charts may be misleading in a population that is short because of GH deficiency and spinal irradiation, and with pubertal maturation delay [10]. In adults, other femoral and distal radial sites may be used, but corrections should still be made for size [10]. Volumetric densities, independent of bone size and measured with quantitative computed tomography, are the current 'gold standard' [78].

In children with newly diagnosed cancer [79] or leukaemia [45], two longitudinal studies documented negative bone turnover at diagnosis, decreases in Vitamin D metabolites [79] and GH resistance [45]. The resulting impaired accrual of cortical (femoral neck), but not trabecular (lumbar spine) bone [79] recovered with disease remission. Prospective studies like these help delineate the multifactorial aetiology of peak bone mass impairment and encourage appropriate intervention strategies.

8. Obesity

Excessive weight gain is a recognised complication of suprasellar, but not intrasellar, tumours and their treatment. For some time, growth may be maintained in the face of GH deficiency by increased IGF-bioavailability, modulated in turn by hyperinsulinaemia which further drives the obesity [80]. There is some evidence to suggest that obesity in these circumstances results from ventromedial hypothalamic lesions causing disinhibition of vagal tone at the level of the pancreatic β cell; in extreme cases truncal vagotomy has alleviated the obesity [81].

The tendency to obesity observed in cranially-irradiated youngsters without hypothalamic lesions is harder to explain [65,82] and just as difficult to treat. Whether the eventual insulin resistance is also primarily the result of increased vagal tone or secondary to hyperphagia involving central satiety centres is unknown. Recent work suggests that survivors of leukaemia have decreased metabolic expenditure, rather than increased metabolic intake, entirely due to reduced physical activity [83]. Corticosteroid use may also be an important contributory factor. In studies so far, cortisol secretion appears normal in childhood [75], but in adults with prolonged GH deficiency syndrome, there may be a change in the bioavailability of cortisol through 11β-hydroxy-steroid dehydrogenase and the cortisol-cortisone shuttle [84].

Obesity and insulin resistance pose a real risk of premature death from diabetes and cardiovascular disease. GH deficiency aggravates obesity, whilst GH therapy decreases fat mass, increases lean mass through direct actions on adipocytes and suppresses leptin in parallel [66]. Both insulin and leptin are suppressed by somatostatin which paradoxically, may improve short term insulin resistance in this situation [83]. Leptin signalling modulates energy balance via effects on the hypothalamus and other tissues, maintaining adipose tissue mass within a finite physiological range. Any role that disturbances in this pathway might play in the evolution of obesity (or early puberty) after cranial irradiation remains still to be elucidated, but 'healthy life-style' measures and adult GH replacement therapy need to be considered in these circumstances, even if there are no other significant endocrinopathies.

9. Growth hormone therapy and tumour relapse

The risk that *r-h*GH may predispose to malignancy or relapse [85,86] is only theoretical [87,88], at least when used in replacement doses, although very large numbers of GH-treated individuals would have to be studied to achieve statistical certainty. There are reports of acute leukaemia in GH-treated children, but half had predisposing conditions, and leukaemia has also been reported in *un*treated patients with idiopathic GH deficiency [89]. Although lymphocyte subsets are normal in GH-deficient patients, consistent with the absence of clinical immunodeficiency, lymphocyte natural killer activity is reduced in some individuals [90]. GH receptors are present on lymphocytes. If leukaemic transformation has

already taken place, GH might accelerate the process, but the concentrations needed are 10 times higher than those used therapeutically [85]. Amongst 6284 GH-treated individuals in the USA with 59 736 patient years of follow-up, just 3 cases of leukaemia occurred Relative Risk (RR) 1.8, 95% Confidence Interval (C.I.) 0.8–7.5). This figure increased to 6 cases at 83,917 patient years of follow-up (RR 2.6, 95% C.I. 1.2–5.2), but 5 of these patients had previous cranial tumours and all except one had been pretreated with cranial irradiation [87]. Further reassuring evidence comes from a rodent tumour-bearing model whose GH-induced improvement in nitrogen-wasting and cachexia was not at the expense of an increase in primary tumour size; there was a surprising reduction in the size and number of pulmonary metastases compared with placebo-treated animals [91]. Nevertheless, supraphysiological doses should be used rarely and only with extreme caution in the clinic.

To achieve a maximum response to therapy, *r-h*GH should be substituted early, before (an age-appropriate) puberty. However, most centres are cautious about introducing this therapy within the first 1–2 years after cancer treatment as this is the time of highest relapse rate. By pharmacological testing, most children treated for brain tumours will be deficient within that time. However, the diagnosis may be delayed or difficult in children treated with lower cranial irradiation doses for leukaemia because of the discrepancies discussed in a previous section. It is therefore paramount carefully to document growth (sitting and standing height), weight and pubertal status 3–6 months from cancer diagnosis until adult height, and also to measure parental heights. Growth and growth velocity must be carefully interpreted in the light of mid-parental target height, the tendency to early puberty, advanced skeletal maturity, inexorable weight gain and previous therapy (e.g. spinal irradiation with/without chemotherapy). The smallest, youngest and most intensively treated children are particularly at risk of failing to achieve an adequate adult height even with *r-h*GH replacement. Supportive evidence of GH deficiency, from pharmacological (glucagon or insulin-hypoglycaemia) or physiological tests, is invariably required for licensing purposes, especially as radiation treatments become more focused and refined. Nevertheless, there may be instances where tests are not confirmatory and further physiological assessment or even a therapeutic trial of *r-h*GH may be necessary.

10. Summary

Cranial irradiation to the HPA usually results in dysfunction. Its incidence, time course and severity—as indicated by the number of affected anterior pituitary hormones—are dependent not only on the dose, fractionation and time elapsed since irradiation, but also on the innate hierarchical sensitivity of each hormone and the site of any disease. Irradiation is not the only culprit. Tumour position, surgery and chemotherapy also contribute to late toxicity at all levels of the hypothalamo–pituitary–target gland axis. If tumours have not involved the 'central' pituitary area, the GH axis is the most sensitive and the adrenal axis the most resistant to the effects of direct irradiation. Since endocrinopathies may evolve over many years, lifelong endocrine follow-up, in an age-appropriate multidisciplinary setting, is necessary after cranial irradiation.

Difficulties in interpreting growth rates of children with radiation-induced skeletal lesions and in evaluating the GH and ACTH responses to pharmacological stimuli make it important to define the pathophysiology of postirradiation endocrinopathies. With better understanding of the neuroregulatory control of hormonal secretion this is now a priority, because it will help target potential protective strategies as well as the most appropriate replacement therapy. Instituting therapy early, before clinical symptoms, may be of especial benefit in terms of normal pubertal and social adjustment, growth, fertility and bone mineralisation.

GH replacement therapy has been traditionally discontinued after the end of adolescence. However, an increasing number of reports suggest an important role for GH on atherogenic lipid profiles, body mass and bone density as well as quality of life (QoL). Replacement therapy may have to be continued indefinitely at lower doses for longer, particularly in older patients and those with multiple endocrinopathies. Because of the potential hazards of indiscriminate replacement therapy and real concerns about GH mitogenicity, it becomes all the more important to establish accurate normal ranges for pharmacological and physiological tests of GH release at all ages and to understand the factors implicated in their action. More resources need to be allocated to encouraging a healthy, active life-style and increased metabolic expenditure, perhaps delaying the need for adult GH replacement in those with isolated GH deficiency.

Recognition of the precise causes and evolutionary changes leading to neuro-endocrine sequelae will greatly assist oncologists and radiotherapists in planning their treatment protocols to reduce morbidity and prolong survival. The new challenge of addressing the causes of obesity and hyperinsulinaemia, defining the aetiology of premature puberty and attempting to preserve fertility and improve psychosocial and neuro-rehabilitation will ensure that paediatric endocrinologists and oncologists continue to work closely together in a multidisciplinary setting for the foreseeable future.

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