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# Hypothalamo-Pituitary-Adrenal Axis Integrity After Cranial Irradiation for Childhood Posterior Fossa Tumours

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***Background.*** The evolution of anterior pituitary deficits after treatment for pituitary tumours has been largely attributed to local irradiation, but may be influenced as much by tumour mass or surgery. Other than growth hormone (GH) insufficiency, the late endocrinopathies after survival from non-central brain tumours have been little documented. The aim of this study was to investigate the hypothalamic-pituitary-adrenal (HPA) axis in long-term survivors of cranial irradiation for childhood posterior fossa tumours. ***Procedure.*** We studied long-term data in patients treated prepubertally for posterior fossa brain tumours and systematically referred by radiation oncologists for growth and pubertal monitoring to the London Centre for Paediatric Endocrinology over the last 25 years. They must have undergone HPA axis assessment twice, first prepubertally at documentation of growth failure, and second at completion of growth and puberty. Data on sixteen patients (12 males, 4 females; median age: 5.7 years, range: 2.5–8.8 years), who had undergone excision surgery with high dose cranial irradiation and/or chemotherapy for childhood posterior fossa tumours, were examined. Patients were followed for a median of 11.0 (range: 6.8–21.4) years after radiotherapy. HPA axis assessment was undertaken with the insulin-induced hypoglycaemia test (ITT). Basal thyroid, cortisol and gonadal function tests were undertaken annually throughout the follow-up period and any deficits replaced. ***Results.*** At each ITT, all patients mounted an inadequate GH response. By the end of the follow-up period all patients remained severely GH deficient, two (12.5%) had partial ACTH insufficiency, one (6.3%) had secondary hypothyroidism but none were gonadotropin deficient or hyperprolactinaemic. ***Conclusions.*** Unlike the severe, evolving multiple pituitary deficits after treatment of pituitary or central tumours in adults, these findings in children with posterior fossa tumours suggest that, with the exception of GH, neurotoxicity due to irradiation *per se* is associated with a low prevalence of anterior pituitary hormone deficiencies, even at a long follow-up. Since the children in this study were selected for assessment on the basis of growth failure, the high prevalence of GH insufficiency at first testing is to be expected; however, the early onset (within 1–3 years of irradiation) and permanence we have identified supports the view that GH is the most sensitive hormone to radiation injury.
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**Key words:** HPA axis function; post-irradiation effects; posterior fossa tumours

## INTRODUCTION

The effects of radiotherapy and chemotherapy are widely recognised to be relevant to the adverse neuropsychological and endocrine outcomes of children treated for medulloblastomas, and attempts to reduce therapeutic intensity are increasingly being made [1]. Arguably, however, these treatments may be no more important as determinants of functional outcome than the tumour itself, peri-operative morbidity, and psychosocial adversity, the 'dose' and timing of which are more difficult to measure. The apparent cognitive advantage of children treated with lower doses of cranial irradiation, perhaps at the expense of long-term cure, has only been documented in cross-sectional studies of an incomplete, and possibly self-selecting, sample of treated children whose follow-up was short. The longitudinal data in these studies do not confirm the benefit of reduced dose irradiation [2,3].

The development of anterior pituitary deficits in post-operative adult patients undergoing external radiotherapy for pituitary or closely related tumours is dose- and fractionation-dependent and evolves over time. All are growth hormone (GH) deficient within 5 years of a median pituitary dose of 40Gy (delivered as 15, 2.6Gy fractions over 3 weeks) and 80% or more experience ACTH and gonadotropin deficiency at a median 5 year follow-up [4,5]. Paradoxically, however, GH appears to be the only reported endocrinopathy in the large majority of cross-sectional and retrospective studies in cranially irradiated childhood survivors of non-central brain tumours [6–8]. Cross-sectional rather than longitudinal assessments, differences in treatment techniques, follow-up times, tumour position, patient age and methods used to test the

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hypothalamic-pituitary-adrenal (HPA) axis integrity, may have contributed to these discrepancies.

Determining the aetiology of any tumour- or treatment-related neurotoxicity carries implications for future therapies aimed at reducing morbidity without compromising a 70% survival [1]. Therefore, the aim of the present study was to retrospectively investigate the integrity of the HPA axis in survivors of similar treatment schedules for posterior fossa tumours as prepubertal children, all of whom had been followed longitudinally 6 monthly from the end of radiation therapy, at least to growth completion.

## MATERIALS AND METHODS

Of 140 patients with tumours of the central nervous system referred systematically in the last 25 years to the London Centre for Paediatric Endocrinology for growth assessment after cranial (with/without spinal) irradiation, we identified a cohort of sixteen (12 males, 4 females) patients with posterior fossa tumours, who had undergone provocative anterior pituitary stimulation tests both at prepubertal demonstration of growth failure (median age: 7.7 years, range: 5.0–10.1 years), one to three years after curative radiotherapy, and at discontinuation of treatment with recombinant human growth hormone (*r-h*GH), after completion of growth and puberty (median age: 15.5 years, range: 12.3–26.1 years). The latter policy of routine re-testing, was commenced only in 1995/96 when *r-h*GH therapy was licensed for use in GH-deficient adults. Given our selection criteria, all patients had decreased prepubertal growth velocity at presentation, sufficient to warrant HPA axis assessment.

The tumours had been diagnosed at a median age of 5.7 (range: 2.5–8.8) years. Histological examination confirmed the diagnosis of medulloblastoma in twelve patients, low-grade astrocytoma in three and ependymoma in one patient.

Following tumour resection, patients received neuraxial (30Gy) radiotherapy from a $Co^{60}$ source in 18–20, 1.6–1.8Gy fractions and a 20Gy posterior fossa boost in 20, 1Gy fractions. The estimated dose to the HPA axis was at least 40Gy giving a biologically effective dose of 77.4Gy (range: 70.8–91.7Gy) [9]. The youngest five patients (<5 years) all additionally received adjuvant chemotherapy, which included potentially gonadotoxic nitrosoureas.

HPA axis assessment was undertaken with insulin-induced (0.1 u/kg) hypoglycaemia testing (ITT) twice, to achieve either a glucose nadir of <2.5 mmol/L and/or a 40% drop from baseline values [10]. These tests were performed at documentation of growth failure and at completion of growth and puberty, at a median of 1.3 (range: 0.5–2.5) years and 9.2 (range: 6.5–14.6) years after radiotherapy, and aged 7.7 (5.0–10.1) and 15.7 (12.3–26.1) years, respectively. All patients were treated with *r-h*GH for growth failure, with good response. Basal thyroid, cortisol and gonadal function tests were undertaken annually, or if symptomatic, throughout the total follow-up period of 11 (range: 6.8–21.4) years.

### Assays

**Growth hormone.** At first ITT, serum GH was measured with the Hybritech immunoradiometric assay (Hybritech, Liege, Belgium). The sensitivity of the assay was 0.5 mU/L with inter- and intra-assay coefficients of variation (CVs) less than 10.5%. After 1995, when the second ITT was performed, the North East Thames Regional Immunoassay (NETRIA) immunoradiometric assay was used, with sensitivity less than 0.5 mU/L and inter- and intra-assay CVs less than 5%.

**Cortisol.** Prior to 1993, serum cortisol concentrations were measured using the Farmos radioimmunoassay (Farmos Diagnostica, Farmos Group, SF-20101 Turku, Finland) with sensitivity of 5 nmol/L. The intra-assay CVs were 4.6 and 1.7% at serum concentrations of 70 and 329 nmol/L, respectively. The inter-assay CVs were 6.2 and 5.3% at serum concentrations of 71 and 325 nmol/L, respectively. Between 1993 and 2000, cortisol concentrations were measured using the Abbott RIA (Abbott Laboratories, Diagnostics Division, Abbott Park, 60064, IL), with a sensitivity of 10 nmol/L. The intra-assay CVs were 3.7 and 5.2% at serum concentrations of 106 and 274 nmol/L, respectively. The inter-assay CVs were 9.2 and 6.7% at serum concentrations of 110 and 414 nmol/L, respectively.

**Other measurements.** Serum T4, TSH, PRL and gonadotropin concentrations were measured using conventional radioimmunoassays.

## RESULTS

At each ITT, all patients achieved adequate hypoglycaemia (plasma glucose <2.5 mmol/L) but mounted an inadequate peak GH response (<13.5 mU/L) in our Hybritech assay [11]. They consequently received *r-h*GH early to augment the prepubertal and largely sub-ischial component of childhood growth whilst possible. The ultimate growth response was compromised, as expected, by their recognised early puberty, at 10.4 (9.6–11.1) years for boys and 9.3 (7.7–10.8) years for girls, and spinal irradiation, together limiting the pubertal growth spurt [12]. Median pre-treatment and adult height standard deviation (SD) scores were −0.21 and −0.22, respectively, sitting height SD scores −0.39 and −1.02, respectively, and subischial length SD scores were −0.53 and −0.34, respectively, suggesting at least maintenance of the normal pre-treatment position without further accruing height deficits due to undiagnosed GH deficiency, late treatment or vertebral damage from spinal irradiation. At re-testing, at completion of growth and puberty, all

**TABLE I. Clinical Characteristics and Biochemical Findings in the 16 Subjects**

| | | | | 1st HPA axis assessment (ITT) | | | 2nd HPA axis assessment (ITT) | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient no. | Sex | Age (years) | Tumour | $GH_{peak}$ (mU/L) | $Cortisol_{basal}$ (nmol/L) | $Cortisol_{peak}$ (nmol/L) | $GH_{peak}$ (mU/L) | $Cortisol_{basal}$ (nmol/L) | $Cortisol_{peak}$ (nmol/L) |
| 1 | M | 7.4 | Medulloblastoma | 10.6 | 309 | 556 | 3.2 | 643 | 643 |
| 2 | M | 2.5 | Medulloblastoma | 3.7 | 282 | 692 | 1.0 | 296 | 967 |
| 3 | M | 3.5 | Medulloblastoma | 4.3 | 172 | 768 | 8.1 | 644 | 651 |
| 4 | M | 5.0 | Medulloblastoma | 1.9 | 450 | 837 | 0.3 | 553 | 442 |
| 5 | M | 7.8 | Medulloblastoma | 13.3 | 223 | 650 | 3.5 | 473 | 584 |
| 6 | F | 6.4 | Medulloblastoma | 12.1 | 269 | 843 | 2.0 | 402 | 384 |
| 7 | M | 3.0 | Medulloblastoma | 2.1 | 264 | 631 | 0.9 | 307 | 504 |
| 8 | M | 8.8 | Medulloblastoma | 2.3 | 382 | 680 | 12.0 | 484 | 647 |
| 9 | F | 5.2 | Astrocytoma | 6.0 | 206 | 326 | 1.7 | 254 | 354 |
| 10 | M | 7.3 | Medulloblastoma | 7.2 | 375 | 580 | 5.3 | 547 | 745 |
| 11 | M | 6.3 | Ependymoma | 5.8 | 267 | 593 | 0.6 | 551 | 556 |
| 12 | M | 3.6 | Astrocytoma | 7.4 | 206 | 687 | 1.4 | 157 | 674 |
| 13 | F | 4.7 | Medulloblastoma | 4.6 | 508 | 892 | 9.0 | 332 | 658 |
| 14 | M | 6.2 | Medulloblastoma | 9.2 | 195 | 580 | 2.2 | 324 | 503 |
| 15 | M | 6.2 | Astrocytoma | 0.5 | 176 | 957 | 2.8 | 535 | 596 |
| 16 | F | 4.7 | Medulloblastoma | 12.3 | 241 | 804 | 1.7 | 587 | 648 |

patients had severe GH deficiency (<12 mU/L) (Table I) (Fig. 1).

At first ITT, all but one (patient 9) patient had normal cortisol response to a hypoglycaemic stimulus and none was receiving hydrocortisone replacement therapy. At second ITT, basal 08.00h cortisol values ranged from 296 to 644 nmol/L excepting one at 157 nmol/L (Fig. 2). The latter patient had a peak cortisol response to hypoglycaemia of 674 nmol/L. Other peak cortisol responses also remained intact (>500 nmol/L) [13,14] in all but two (12.5%) patients (6 and 9), whilst one (patient 4) had a higher basal than peak cortisol concentration (553 vs. 442 nmol/L). Patient 9 was the only one noted to have had persistently low cortisol responses (peak <350 nmol/L) on both first and second occasions and was subsequently diagnosed to have late-onset 21-hydroxylase (CYP21) deficiency as a cause of her adrenal insufficiency, with elevated ACTH concentrations. Patient 6 had satisfactory basal 08.00h cortisol values >400 nmol/L, unlikely to indicate adrenal insufficiency in either an insulin-hypoglycaemia test [14] or low dose ACTH stimulation test [15]. Both patients 4 and 6 further revealed normal peaks (>500 nmol/L) and incremental (>200 nmol/L) cortisol responses to low dose ACTH stimulation tests (500 ng/1.73 $m^2$) [16]. Neither has required glucocorticoid replacement to date (Table I) (Fig. 2). Two more patients (7 and 14) had borderline peak responses to hypoglycaemia (503 and 504 nmol/L) but both of these had basal 08.00h

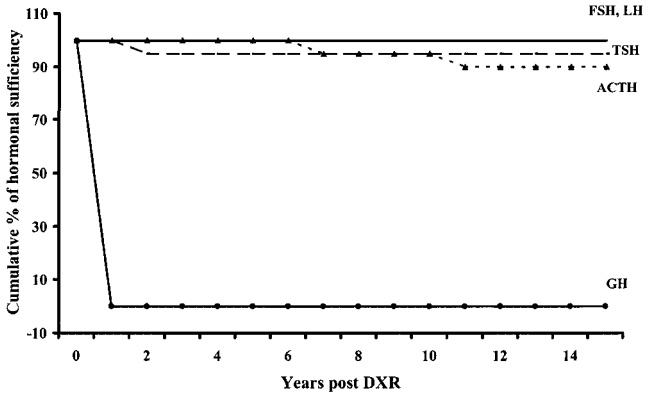


**Fig. 1.** Cumulative percentage of patients with normal anterior pituitary function during the follow-up period, which ranged from 6.8 to 21.4 years (median: 11 years). Duration of follow-up was greater than 8 years in 13 patients, more than 12 years in 7 patients and 16 years in one patient. The prevalence of early GH insufficiency in this study may be overestimated due to the selection bias, but its permanence, once present, is noteworthy. With the exception of GH, anterior pituitary deficiencies were rare.

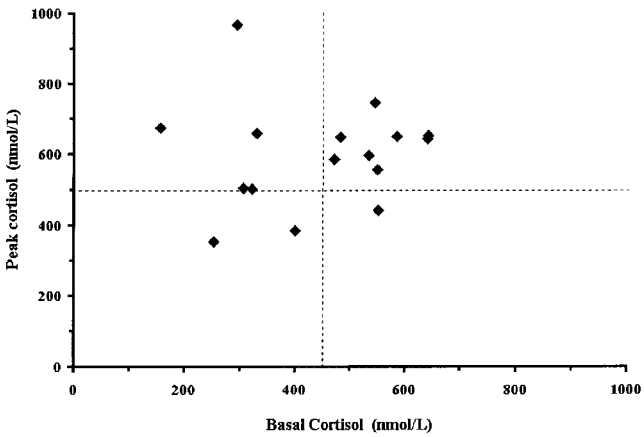


**Fig. 2.** Basal cortisol concentrations and peak cortisol responses to 2nd ITT in all subjects.

levels >300 nmol/L and incremental responses to low dose ACTH stimulation test >200 nmol/L.

Another patient (6.3%) developed secondary hypothyroidism 1.7 years after irradiation. Primary hypothyroidism was detected in four (25%) at 3.3 (range: 1.6–6.9) years after radiotherapy. Two patients (12.5%), both of whom had received adjuvant chemotherapy with known gonadotoxic agents [17], had gonadal dysfunction evidenced by elevated gonadotropin concentrations peripubertally. All were appropriately replaced prior to second ITT. There was no case of gonadotropin insufficiency or hyperprolactinaemia in our patients (Fig. 1).

## DISCUSSION

Cranial irradiation and neuraxial prophylaxis remain the only proven curative therapy in malignant brain tumours of childhood, with 5 year survival rates at 60–70% [18]. This is at the expense, however, of significant late neural [2,3] and endocrine toxicity [4,5,7,19,20] mostly blamed on a dose-dependent effect of cranial irradiation [2] causing an evolving hierarchical loss of all post-operatively intact anterior pituitary hormones, in which GH is the most vulnerable and TSH the most resistant hormone [4,8]. The contribution of chemotherapy, tumour- or surgically-induced late damage has not been considered significant and is more difficult to study.

The anterior pituitary deficits seen in adults irradiated post-operatively for pituitary tumours have been attributed entirely to irradiation [4,20], but few patients (18–21% of 165 patients) in these studies had entirely intact pituitary function before irradiation. Only 23 of 124 (18.5%) had normal GH, 34 of 165 (21%) had normal LH and FSH, whilst more (57 and 80%, respectively) had normal ACTH and TSH secretion. The prevalence of dysfunction with time was calculated annually for each individual hormone, rather than exclusively for those with entirely intact HPA function, to a median follow-up of just 5 years [4]. The older patients (mean age: 48 years) and the natural decline in GH secretion with age [21] may have influenced the diagnostic criteria for GH deficiency. Lower ''cut-offs'' have since been recommended for adults [22] than in children or adolescents [11].

With the exception perhaps of GH, where the few longitudinal studies of stimulated [23–25] and spontaneous 24 hr GH secretion [25] suggest subtle and persisting post-operative neuroregulatory disturbances, compounded by irradiation, chemotherapy and time [25,26], the independent neurotoxic effect of cranial irradiation, as distinct from any tumour, surgical or other treatment effect, remains unclear. Although the selection criteria in our study bias our results in favour of the high prevalence of GH deficiency we document, long-term cohort studies in treated children confirm the high incidence and permanence of GH deficiency after cranial irradiation (>85%) for posterior fossa tumours [25,26] and support our findings. However, the prevalence of ACTH insufficiency we document is very much less than in the adult pituitary series [4]. Even after the highest pituitary irradiation doses, Constine et al. [27] reported just 20% prevalence and noted that doses below 50Gy are unlikely to cause non-GH HPA axis impairment.

Others have also noted the low prevalence of endocrinopathies other than GH deficiency (2–6%) after estimated pituitary doses of 40–50Gy, at a similar follow-up time (9.6 years) [7]. However, this series included optic gliomas, the position of which is still very central, whilst a much older study of posterior fossa tumours (with older assays) documented a lower (50%) incidence of late GH deficiency [6]. Hence, it remains unclear whether whole brain irradiation in doses of 30Gy coupled with a 20Gy posterior fossa tumour boost (resulting in consequent pituitary doses of at least 40Gy) has any direct neurotoxic effect on ACTH or other anterior pituitary hormone secretion other than GH.

Although our patients were self-selected for growth failure and thus GH deficiency, our study of cranially irradiated prepubertal children without pituitary masses confirms the early (within 1–2.5 years) post-irradiation GH deficit and its permanence noted in other studies [25,26,30]. In such children with growth failure following irradiation for posterior fossa tumours, we failed to document significant ACTH deficiency requiring therapy, or other anterior pituitary endocrinopathies as noted in the adult pituitary studies [4], despite similar pituitary irradiation (> 40Gy) and biologically effective doses, a younger, more vulnerable nervous system [1,2], and twice the median follow-up period (Fig. 1). This suggests that these consequences are rare if the tumours themselves are displaced from the central axis, even though the pituitary itself falls well within the high dose irradiation field.

The normal cortisol response to insulin-induced hypoglycaemia has been standardised against intra-operative surgical stress as a plasma cortisol concentration >580 nmol/L [13]. However, studies using newer radioimmuno-assays suggest that this value should be lower (519 nmol/L), whilst basal values >450 nmol/L indicate normal adrenal function [14]. Differences between serum or plasma cortisol levels as measured with different kits and methods can be remarkable [28], ''cut-off'' levels of 526 and 600 nmol/L being identified in serum and plasma, respectively [29]. We have clinically used a peak serum cortisol of 500 nmol/L to define normality for hypoglycaemia in keeping with similar normative values obtained in our laboratory to low dose synacthen stimulation tests [16].

An alternative explanation for our discrepant results to those of Littley et al. [4] is the potentially greater biological effectivity of the same total dose if larger

fractions (>2Gy) are used [9,31], thus causing earlier evidence of damage in the adult study. However, the young brain is known to be particularly vulnerable to irradiation-induced neural toxicity [2] despite the standard use of smaller (1.6–1.8Gy) fraction sizes. We saw no such significant deficit even in those children followed longest (upto 21 years). A study of adult patients irradiated for prolactinomas also used smaller fraction sizes (45Gy in 25, 1.9Gy fractions over 35 days) to a similar total dose and similarly failed to detect any ACTH or TSH deficiency [32]. Pituitary irradiation experiments in rats also failed to confirm significant ACTH or gonadotropin insufficiency, whereas TSH secretion—relatively preserved following surgical cure of GH-secreting [33] or non-functioning adenomas [34]—is paradoxically affected early, soon after GH and prolactin [35]. These latter hormonal patterns after irradiation alone, echo their common developmental signalling cascade [36], suggesting an alternative explanation, perhaps in the form of a developmental or surgical insult.

Surgery is considered a specific and discrete pituitary insult. Although there have been no studies to address the role of surgery in the development of late endocrinopathies, one may hypothesise that pituitary recovery may follow relief of mass compression [33,34,37] as pituitary-portal compression is relieved [34]. Also, slowly replicating neural cells may not at first demonstrate damage but eventual cell replication failure may result, and pituitary dysfunction may become apparent over time. The resulting endocrinopathy may thus be due as much to delayed evidence of earlier tumour- or surgery-induced neuronal injury as to subsequent superimposed irradiation.

Attempts to delay or avoid radiation, and to reduce its dose intensity or fraction size in the hope of reducing neurotoxicity [1,2], endocrinopathies and infertility [20], is increasingly being proposed, particularly in the youngest (<3 years) and most vulnerable, by substituting adjuvant post-operative chemotherapy. However, this may be at the expense of significant cure [38,39], and possibly additive neuropsychological, neuroradiological [40] and neuroendocrine [25] toxicity after salvage therapy.

The distinction between late neural toxicity due to tumour/disease or surgery and that due to irradiation therapy is therefore important. Current management of children with posterior fossa tumours is based on the assumption that virtually all neurotoxicity is irradiation-induced [1]. We challenge that assumption on the basis of surprisingly preserved hypothalamic-adrenocorticotrophic function in long term survivors of pituitary irradiation without pre-existing tumour-related and/or surgical lesions in the area. We also may reassure physicians that hypopituitarism is unusual after this type of therapy, making testing the HPA axis for anything other than GH deficiency unnecessary in the asymptomatic, cranially irradiated child, even in the long term, provided there is no centrally placed disease. We also suspect the same might be true of similar, smaller pituitary fractionation schedules in adults and that surgery or the tumour itself may be the greater culprit here.

In summary, these studies of neuroendocrine function undertaken before and after cranial irradiation for childhood posterior fossa tumours have shown that, with the exception of GH insufficiency, significant long-term hypopituitarism is rare. The previously reported high prevalence of ACTH and other late neuroendocrine deficits in adult patients most probably reflects confounding and evolving late tumour- or surgery-induced neuronal damage rather than simple irradiation-induced toxicity.

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