Irradiation-induced hypopituitarism in adult brain tumour survivors: single-centre longitudinal data

Nikolaos Kyriakakis[1], Julie Lynch[1], Susan C. Short[2], Paul Hatfield[2], Carmel Loughrey[2], Georgina Gerrard[2], Steve M. Orme[1] & Robert D. Murray[1]

[1]Leeds Centre for Diabetes & Endocrinology, St James's University Hospital, Leeds, UK
[2]Clinical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds, UK

Leeds Centre for Diabetes and Endocrinology

Introduction

Radiation-induced hypopituitarism is a well-recognized complication of cranial radiotherapy (cXRT). The presence and severity of hypopituitarism following cXRT depends on the total radiation dose delivered to the hypothalamo-pituitary (HP) axis, the fraction size, the total duration of the radiotherapy scheme [1] and the duration of follow-up post-irradiation [2]. The frequency of deficits in individual anterior pituitary hormone axes induced by radiation is greatest in the growth hormone axis, followed by gonadotropin, ACTH and TSH axes [3]. To date radiation-induced hypopituitarism has primarily been characterised in childhood cancer survivors. Few data are available for survivors of adult brain tumours. In the largest series to date (n=56), Agha et al (2005) showed hypopituitarism to be present in 41% of patients following a median biologically effective dose of 54Gy. The frequency of GH, ACTH, gonadotropin, and TSH deficiencies was 32%, 21%, 27%, and 9% respectively [4].

Methods

We retrospectively reviewed medical records of patients who received cXRT for primary non-pituitary brain tumours during adulthood and and have been referred for endocrine assessment. Longitudinal data regarding pituitary-related treatment outcomes were collected. The ITT and/or GST were used to assess GH and HPA axes integrity. Basal values for the additional anterior pituitary hormones were used to determine gonadotropin, TSH and prolactin status. Patients with known HP axis dysfunction prior to cXRT were excluded from the study.

Results

107 patients (mean age at cXRT 40.0 13.1 years) with median duration of post-cXRT follow-up of 8 years (IQR 5.3-11 years) were studied. 32.7%, 19.6%, 20.6% and 27.1% of patients had tumours located in the anterior, middle, posterior cranial and central (perisellar) regions respectively. Patients characteristics are shown in Table 1.

Table 1. Details of patients' demographics and baseline clinical characteristics. Results are presented as absolute numbers of patients. Results in brackets represent percentage of the total number of patients.

Characteristic	Patients (%)	Characteristic	Patients (%)
Gender		**Age at XRT (years)**	40 ± 13.1
Male	55 (51.4%)	**Type of tumour**	
Female	52 (48.6%)	Gliomas	60 (56%)
Therapeutic interventions		Meningiomas	22 (20.6%)
Surgery + XRT	54 (50.4%)	PNET	9 (8.4%)
Surgery + XRT + Chemotherapy	34 (31.8%)	Pinealomas	8 (7.5%)
XRT + Chemotherapy	5 (4.7%)	Other primary tumours	8 (7.5%)
XRT only	14 (13.1%)	**Mean number of dynamic pituitary tests per patient**	2.5 ± 1.6
Tumour localization		**Types of dynamic pituitary tests**	
Anterior cranial fossa	35 (32.7%)	ITT only	22 (20.6%)
Middle cranial fossa	21 (19.6%)	GST only	76 (71%)
Posterior cranial fossa	22 (20.6%)	ITT + GST	9 (8.4%)
Central (perisellar) region	29 (27.1%)		

94.4% received fractionated photon radiotherapy of a median dose of 54 Gy (IQR 50.1-54 Gy) while the remaining patients received proton beam or stereotactic radiotherapy. Evidence of any form and degree of pituitary dysfunction developed in 88.8% of the patients during follow-up. The GH axis was the most commonly affected axis with GHD present in 86.9% of patients (severe GHD 64.5%, partial GHD 22.4%), followed by LH/FSH (34.6%), ACTH (23.4%), and TSH (11.2%) deficiencies. Clinically significant ACTH deficiency necessitating glucocorticoid replacement was present in only 10.3% of cases. Hyperprolactinaemia was noted in 15.0% of patients and occurred in females only. Figure 1 summarises the above. Single pituitary axis dysfunction was noted in 41.1% of patients (44/107), while multiple pituitary hormone deficits was present in 47.7% of cases (51/107). Entirely normal pituitary function post cranial irradiation was seen in only 11.2% of our cohort of patients (12/107).

Results (cont'd)

Longitudinal data analysis showed accumulation of pituitary hormone deficits the longer the duration of follow-up post cXRT (Figure 2). The prevalence of severe GHD, LH/FSH, ACTH and TSH deficiencies almost doubled between year 2 and year 7 of follow-up. The majority of hormone deficits developed during the first 5 years post radiotherapy, however late-onset pituitary dysfunction, or progression in the severity of a previously documented hormone deficiency, can still be observed more than 10 years out from treatment.

Figure 1. Prevalence of the pituitary hormones deficiency and hyperprolactinaemia following cranial radiotherapy in individuals diagnosed with adult-onset non-pituitary brain tumour after a mean duration of follow-up of 9.1 years.

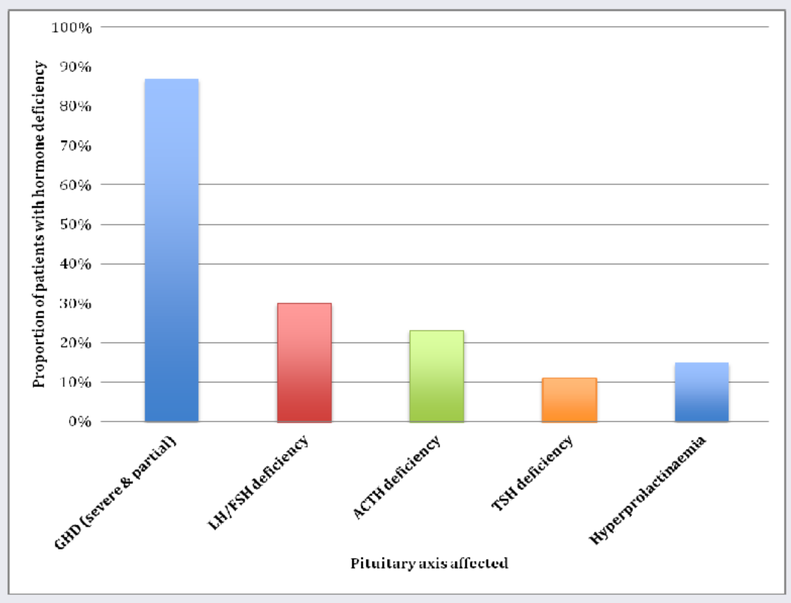
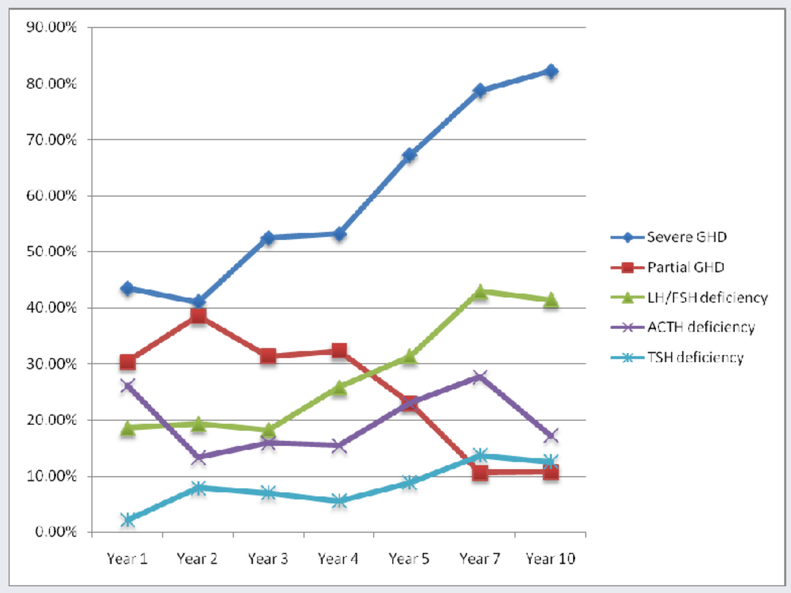


Figure 2. The prevalence of anterior pituitary hormone deficiencies in patients who have received irradiation for non-pituitary brain tumours with time since irradiation. Results are presented as percentages of the patients diagnosed with a pituitary hormone deficiency among the total number of patients who had been followed up until that particular year and had been tested with dynamic and baseline pituitary investigations.



Conclusions

This is the largest cohort to date and with longer mean follow-up post cXRT compared with previous reports. Our results are based on a cohort of patients that were selectively referred to Endocrinology by our Oncology colleagues based on the radiotherapy schemes they underwent. The GH axis was the most radiosensitive in our study, followed by gonadotropins, ACTH and TSH. The incidence of hypopituitarism following cXRT was significantly higher in our cohort (almost 90%) compared with previous studies [4, 5], possibly related to the longer duration of patient follow-up in our study, in keeping with the fact that radiation-induced hypopituitarism is a time-dependent phenomenon [2, 3]. Progression in the incidence and severity of hypopituitarism throughout the follow-up period was also observed. Taking into account advancements in the treatment of brain tumours with improved survival rates, as well as the impaired quality of life reported by brain tumour survivors, early detection and appropriate replacement of pituitary hormones is essential. We suggest that adults diagnosed with non-pituitary brain tumours who receive cXRT should undergo long-term endocrine surveillance.

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Nikolaos Kyriakakis
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