Radiotherapy and Oncology 113 (2014) 102–107

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Late effects in head and neck radiotherapy

Pituitary dysfunction in adult patients after cranial irradiation for head and nasopharyngeal tumours

Natasha M. Appelman-Dijkstra [a,*], Frank Malgo [a], Karen J. Neelis [b], Ida Coremans [b], Nienke R. Biermasz [a], Alberto M. Pereira [a]

[a] Center for Endocrine Tumours Leiden, Department of Endocrinology and Metabolic Diseases; and [b] Department of Clinical Oncology & Radiotherapy, Leiden University Medical Center, The Netherlands

ARTICLE INFO

Article history:
Received 31 January 2014
Received in revised form 17 July 2014
Accepted 22 August 2014
Available online 15 September 2014

Keywords:
Pituitary insufficiency
Radiotherapy
Cerebral tumours
Nasopharyngeal carcinoma
Follow up

ABSTRACT

Background: Pituitary insufficiency after radiotherapy in the hypothalamic pituitary region is a well-known complication. However, endocrine assessments are not incorporated in the follow-up after cranial irradiation for head and neck tumours.

Aim of the study: To evaluate pituitary function in patients cranially irradiated for non-pituitary tumours.

Patients and methods: Evaluation of pituitary function in all available patients treated at our centre with cranial radiotherapy for head and neck tumours.

Results: We included 80 patients. Forty patients were treated for cerebral tumours, 15 for nasopharyngeal tumours, and 25 for different tumours like meningioma or cerebral metastasis. Mean age was 47.5 (18.6–89.7) years. Mean radiation dose delivered at the pituitary region was 56.27 Gy (40.0–70.0). Pituitary insufficiency was present in 16 patients within 2 years after irradiation 23/49 patients (47%) after 5 years and 27/45 (60%) after 10 years and 31/35 patients (89%) after 15 years.

Conclusion: Pituitary insufficiency is highly prevalent in adult patients treated with cranial radiotherapy for head and nasopharyngeal tumours. These prevalence rates are comparable to those observed after radiotherapy for pituitary tumours. Because hormone replacement of endocrine deficits improves quality of life and prevents potential severe complications, such as Addisonian crises, periodical evaluation of pituitary function is advocated.

Radiation-induced pituitary insufficiency is a well-known dose-dependent late sequel of pituitary irradiation for pituitary tumours with prevalence rates of any pituitary insufficiency of approximately 50% after 5 years, and up to 75% after 10 years following a total dose of 40–45 Gy [1–3]. In accordance, when the hypothalamic–pituitary region is within the radiation field, cranial irradiation for non-pituitary tumours may also induce pituitary insufficiency [4]. In children, the high incidence of pituitary insufficiency after cranial irradiation for cerebral or nasopharyngeal tumours, including total body irradiation (TBI) for haematological malignancies, is well established [5–9]. The Childhood Cancer Survivor Study (CCSS) reported one or more endocrinopathies to be present in 43% of children treated for cerebral tumours. Consequently, these children are subjected to structural endocrine surveillance also when reaching adulthood [10].

Currently, guidelines on endocrine surveillance in adult patients are not available. Survival rates for e.g., cerebral and nasopharyngeal tumours have improved substantially by new treatment modalities [11,12]. Therefore, it is likely that an increasing number of adult patients will also be affected by endocrine complications of cranial irradiation. Since complaints of hypopituitarism are generally non-specific, endocrine tests are required for an accurate diagnose of pituitary failure. Endocrine function tests are necessary for diagnosing hypocortisolism or growth hormone deficiency. Growth hormone deficiency however might not be clinically relevant for a patient treated for a malignant tumour since cancer patients generally will not be substituted with growth hormone, although in childhood cancer survivors there was no statistically significant increased overall risk of the occurrence of neoplasms associated with rh-GH exposure [13]. But diagnosing growth hormone deficiency will still be useful since it may serve as an indicator of radiation induced hypothalamic/pituitary damage. In a recent meta-analysis, we have concluded that the low number of adult patient cohorts followed after cranial radiotherapy for non-pituitary tumours with sufficient long-term data and proper

* Corresponding author. Address: Center for Endocrine Tumours Leiden, Department of Endocrinology C7Q, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands.
E-mail address: n.m.appelman-dijkstra@lumc.nl (N.M. Appelman-Dijkstra).

http://dx.doi.org/10.1016/j.radonc.2014.08.018
0167-8140/

dynamic endocrine evaluation precludes strong conclusions on the incidence and prevalence rates of pituitary insufficiency. However, the meta-analysis suggested a high prevalence of any form of pituitary insufficiency, like in children, of 0.66 (95% CI, 0.55–0.76) after cranial radiotherapy for both nasopharyngeal and cerebral tumours [14]. In addition, the time of onset of pituitary failure was documented in only 3 studies [15–17]. The aim of this cohort study was to evaluate the prevalence, and the time of onset, of pituitary insufficiency in adult patients after cranial irradiation for non-pituitary tumours in our centre.

Subjects and methods

The patient registry of the department of radiotherapy was checked for patients who underwent cranial radiotherapy for non-pituitary tumours from 1990 to 2010 with the hypothalamus and/or the pituitary within the radiation field and who received >20 Gy to the hypothalamus–pituitary region ($n = 1504$). We selected a threshold of 20 Gy based on data from historical cohorts indicating that a total dose of 7–24 Gy delivered to the pituitary/hypothalamus region, may cause growth hormone deficiency only, whereas dosages as high as 50–60 Gy will most certainly cause multiple pituitary hormone deficiencies [18]. When alive and not already known to the outpatient clinic of the department of Endocrinology, patients were invited for endocrine testing. Patients were excluded if: (1) radiotherapy was given for pituitary or parasellar tumours, (2) radiotherapy was applied as TBI, (3) pituitary insufficiency was already present before radiotherapy, (4) had a life expectancy of less than 12 months at time of screening. Pituitary functions were checked at first outpatient clinic visit with basal hormone samples and endocrine function tests, afterwards patients were monitored by a standardized protocol (vide infra). In addition we used clinical and amnestic information on their condition prior to radiation. In case of pituitary insufficiency medication was started at the discretion of the treating physician. This study represents a combined analysis of the patients already known at the department of endocrinology and patients from the screening of records of radiotherapy.

Mean applied radiation dose

All files were screened for a calculated/estimated dose to the pituitary/hypothalamic region. For patients irradiated before 2004, the isodose lines plotted on 2D images and on plain X-rays of the skull were used to estimate the pituitary dose. After the introduction of CT based treatment planning in our department CT images were used to read the plotted dose. Since 2007 the planning software gives a calculated dose to the hypothalamic/pituitary region, and mean doses to the pituitary were collected.

Parameters

At baseline disease specific information was extracted from the medical files.

The following parameters were assessed:

Anthropometric parameters: body weight and height were measured. Body weight was measured to the nearest 0.1 kg, and body height was measured barefoot to the nearest 0.001 m. Additional information on medication use, Karnofsky score, IADL score, and co-morbidity was gathered.

Endocrine assessment

Biochemical parameters: IGF-1, GH, TSH, fT4, ACTH, cortisol, LH, FSH, estradiol, testosterone, Sex Hormone Binding Globulin (SHBG), and prolactin concentrations were measured, furthermore general laboratory parameters including renal and liver function and cardiovascular parameters were obtained. Blood samples were taken for laboratory measurements after an overnight fast.

For diagnosing cortisol deficiency we used the following stepwise approach. First a basal cortisol level was performed. When basal cortisol concentrations were <80 nmol/L, in the absence of glucocorticoid use, the diagnosis of hypocortisolism was considered evident and no additional tests were performed [19]. To date, the insulin tolerance test (ITT) remains the golden standard for the evaluation of the HPA-axis [19]. In case of contraindications for the ITT, such as epilepsy or coronary artery disease, alternative dynamic tests such as the corticotrophin releasing hormone (CRH) test ($n = 10$), the metyrapone test ($n = 4$), or the ACTH stimulation test were used as to assess adrenal function [19–23]. The choice for a specific test was made by the treating physician on an individual basis depending on the patient's clinical condition. Cortisol deficiency was defined by a peak cortisol below 0.55 μmol/L, either after insulin-induced hypoglycaemia (glucose nadir <2.2 mmol/l) or after stimulation with 100 mcg CRH. A limited number of patients were tested using metyrapone ($n = 4$) since in the past CRH was not available for some time, two of them were retested with the insulin tolerance test when possible. Metyrapone (30 mg/kg, Metopiron, Novartis Pharma B.V., Arnhem, The Netherlands) was administered orally at midnight. The next morning post absorptive blood samples were obtained for measurement of 11-deoxycortisol, cortisol and ACTH levels. A cut-off value for 11-deoxycortisol of 200 nmol/L was used to define normal adrenal function [20–22]. Growth hormone deficiency was defined by a GH peak response to the insulin induced hypoglycaemia of <3 μg/l or by a GH peak after combined Growth Hormone Releasing Hormone + Arginine-test (GHRH/Arg test) using BMI-adjusted GH cut-offs. [24,25]. When secondary amenorrhoea was present for >1 year in the presence of a low serum estradiol (estradiol 0–200 pmol/L) with normal or low serum levels of FSH and LH, premenopausal women were classified as gonadotropin-deficient. In men, gonadotropin deficiency was defined as a testosterone level <8.0/l with and normal or low serum levels of FSH and LH (FSH 1.5–12.5 U/L; LH 2.0–9.0 U/L). Thyroid-stimulating hormone (TSH) deficiency was defined as free T_4 level below the reference range (<12 pmol/L). Hyperprolactinaemia was defined by a basal serum prolactin level above the reference range (15.0–23 μg/L, for men and women, respectively).

Assays

In patients, serum IGF-1 concentrations were measured. From 1986 to 2005, serum IGF-1 concentrations were determined by RIA (Incstar, Stillwater, MN) with a detection limit of 1.5 nmol/L and an interassay CV less than 11%. IGF-1 was expressed as SD score for age- and gender-related normal levels determined in the same laboratory. Since 2005, serum IGF-1 concentrations (nmol/L) were measured using an immunometric technique on an Immulite 2500 system (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The intra-assay variations at mean plasma levels of 8 and 75 nmol/L were 5.0% and 7.5%, respectively. IGF-1 levels were expressed as SDS, using lambda-mu-sigma smoothed reference curves based on 906 controls [26,27].

FT4, TSH, LH, FSH, and PRL concentrations were measured by electrochemiluminescence immunoassay (ECLIA), using a Modular E170 (Roche Diagnostics). The maximal inter-assay CV was 5.0%. ACTH was determined by immunoluminometric assay using an Immulite 2500 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The maximal inter-assay CV was between 5.0% and 10.0%. For the measurement of estradiol, a RIA (Orion Diagnostica, Espoo, Finland) was used (CV was 6% at 70 pmol/l) with a detection limit of 20 pmol/l. Testosterone was measured using an RIA (Siemens