Long-term anterior pituitary function in patients with paediatric Cushing’s disease treated with pituitary radiotherapy

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Abstract

Background/objective: Pituitary radiotherapy (RT) is an effective second-line treatment for paediatric Cushing’s disease (CD). Although the short-term effects of pituitary RT are well documented, there are less data on possible long-term sequelae. We report the long-term anterior pituitary function in a cohort of paediatric CD patients treated with pituitary RT.

Patients and methods: Between 1983 and 2006, 12 paediatric CD patients (10 males and 2 females) of mean age 11.4 years at diagnosis (range 6.4–17.4) underwent second-line pituitary RT (45 Gy in 25 fractions), following unsuccessful transsphenoidal surgery. Out of 12, 11 patients were cured by RT (cure interval 0.13–2.86 years) defined by mean serum cortisol of <150 nmol/l on 5-point day curve and midnight sleeping cortisol of <50 nmol/l. Long-term data are available for six male patients, who received RT at the age of 7.0–17.6 years. The mean follow-up from the completion of RT was 10.5 years (6.6–16.5).

Results: At a mean of 1.0 year (0.11–2.54) following RT, GH deficiency (peak GH <1–17.9 mU/l) was present in five out of six patients. On retesting at a mean of 9.3 years (7.6–11.3) after RT, three out of four patients were GH sufficient (peak GH 19.2–50.4 mU/l). Other anterior pituitary functions including serum prolactin in five out of six patients were normal on follow-up. All the six patients had testicular volumes of 20–25 ml at the age of 14.5–28.5 years.

Conclusion: This series of patients illustrates the absence of serious long-term pituitary deficiency after RT and emphasises the importance of continued surveillance.

Introduction

Cushing’s disease (CD) is characterised by hypercortisolaemia secondary to a corticotrophin-secreting pituitary adenoma (1–3). In the paediatric age group, CD is more common in males (4) and can present a difficult diagnostic challenge, as signs and symptoms can be variable and subtle (5). The increasing incidence of childhood obesity may make the diagnosis even more difficult.

Despite advances in the understanding and treatment of CD, the condition still carries with it significant morbidity and mortality (5–7). The management of this condition requires a multidisciplinary approach involving neurosurgeons, endocrinologists, biochemists, radiologists and radiotherapists. The close co-operation between paediatric and adult endocrine teams has proven invaluable in most centres (1–3). The accepted first-line treatment of paediatric and adult CD is transsphenoidal surgery (TSS) with selective microadenomectomy (3, 8, 9), with cure rates for paediatric CD being reported as between 45 and 98% (3, 10–13), depending on the definition of cure. However, a proportion of children will not necessarily be cured with TSS and require second-line treatment (8, 10).

Radiotherapy is recognised as an effective second-line treatment modality in paediatric CD (11, 14, 15). The alternative treatments, namely bilateral adrenalectomy or repeated TSS, carry significant risks of complications including Nelson’s syndrome and permanent pituitary deficiencies respectively (10, 16). The possible sequelae of pituitary radiotherapy (RT) include visual impairment, radiation oncogenesis and late hypopituitarism; however, due to advances in the understanding of the radiobiological effects, these first two complications are fortunately very rare (17, 18). On the other hand, anterior pituitary hormone deficiencies have been well documented following RT to the head and neck when the hypothalamo–pituitary region falls within the radiation field (17). There are few published data on the frequency of long-term anterior pituitary hormone deficiencies post-RT for paediatric CD. The outcome of pituitary irradiation in CD has been reported in a number of small studies with hypopituitarism being a...
recognised complication (18–20). Storr et al. (11) previously described the efficacy of RT in seven children treated by pituitary RT post-TSS in our centre, but the follow-up was relatively brief in terms of other pituitary deficiencies. In the present retrospective analysis, we report the results of anterior pituitary function in six patients treated with pituitary irradiation after more than 6 years follow-up.

**Subjects and methods**

**Patients**

Between 1983 and 2006, 32 paediatric CD patients (21 males and 11 females; mean age, 12.5 years; range, 6.2–17.8 years) were investigated and treated at St Bartholomew’s and The Royal London Hospitals (London, UK). TSS was performed in 31 patients. Bilateral adrenalectomy was undertaken in one patient due to the severity of his disease. Twenty patients had post-operative cure (serum cortisol < 50 nmol/l). Twelve patients (ten males and two females; mean age at diagnosis 11.4 years; range 6.4–17.4) remained hypercortisolaemic in the immediate post-operative period. All 12 patients underwent pituitary RT following unsuccessful TSS. The diagnosis of CD was made on the basis of detectable serum adrenocorticotropic hormone (ACTH), elevated sleeping midnight cortisol of > 50 nmol/l, failure to suppress cortisol during a low-dose dexamethasone suppression test and suppression of cortisol by more than 50% of the baseline values during high-dose dexamethasone suppression test. In addition, patients had an exaggerated response of serum cortisol during a corticotrophin-releasing hormone test (21).

**Response to radiotherapy**

Eleven patients (nine males and two females) were cured after RT (cure interval 0.13–2.86 years) as defined by mean serum cortisol of < 150 nmol/l on 5-point day curve and midnight sleeping cortisol of < 50 nmol/l as previously reported (11). Data of > 5 years follow-up were available for six male patients who received RT at the age of 7.0–17.6 years (Table 1). The mean follow-up from RT was 10.5 years (range 6.6–16.5).

**Indication for radiotherapy**

Pituitary RT was performed at an interval of 0.1–0.7 year following attempted selective microadenomectomy. Evidence of failure of cure by TSS was a post-operative circulating cortisol > 50 nmol/l. In the six patients described here, the 0900 h serum cortisol ranged from 269 to 680 nmol/l during an interval of 4–20 days post-TSS.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age at presentation (years)</th>
<th>Interval between RT and cure (years)</th>
<th>Follow-up post-RT (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>16.6</td>
<td>0.87</td>
<td>11.3</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>6.4</td>
<td>0.92</td>
<td>7.9</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>13.7</td>
<td>0.26</td>
<td>16.5</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>17.4</td>
<td>0.13</td>
<td>7.6</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>7.6</td>
<td>2.86</td>
<td>13.0</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>9.4</td>
<td>0.84</td>
<td>6.6</td>
</tr>
</tbody>
</table>

**Pituitary radiotherapy**

All patients received external beam irradiation, with 6 MV photons from a linear accelerator to deliver 45 Gy, in 25 fractions, over 35 days. A three-field technique (two lateral and one superior oblique) was used to localise radiation to the pituitary as previously described (22).

**Endocrine assessment**

The mean age at the time of long-term GH assessment in four out of six patients was 23.5 years (range 17.7–28.5). Peak growth hormone (GH) secretion was assessed during either an insulin tolerance test (ITT; 0.15 U/kg insulin i.v.) or a glucagon stimulation test (15 mg/kg i.m.). Growth hormone deficiency (GHD) in childhood was defined as peak GH on provocations testing of < 20 mU/l. Severe GHD in paediatric and adult patients was defined as peak GH level ≤ 9 mU/l (23). Prolactin (PRL), luteinising hormone (LH), follicle-stimulating hormone (FSH), ACTH, thyroid-stimulating hormone (TSH), thyroxine (T4), cortisol, testosterone (T) and sex-hormone binding globulin (SHBG) levels were measured at regular intervals during follow-up, with the latest assessment performed at a mean age of 22.7 years (range 14.8–30.4).

**Hormone assays**

GH, ACTH and SHBG were measured using two-site chemiluminescent immunometric assays on an Immulite semi-automated analyser (DPC Ltd, Llanberis, Wales, UK). Assay imprecision for all assays is < 8% (24). Serum cortisol, T4 (free and total), TSH, PRL, LH, FSH and testosterone were determined historically on the Bayer Technicon Immuno-I automated immunoassay analyser (Bayer Diagnostics) and since 2004 on the Roche E170 automated immunoassay analyser. Assay imprecision for the assays on both systems has been < 6%.

**Pubertal assessment**

Assessment of puberty was carried out according to the criteria of Tanner (25). Four patients were pre-pubertal (testicular volume < 4 ml) and two were pubertal at the time of RT (Table 3).

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Results

Growth hormone secretion

Peak GH levels at a mean of 9.3 years (7.6–11.3) post-RT are shown in Table 2. After completion of RT, five out of six patients were GH deficient and received GH therapy. Long-term GH assessment showed recovery in two patients (patients 3 and 5), maintenance of normal GH secretion in one patient (patient 4) and continuation of GHD in one patient (patient 1) (Table 2).

Pituitary–gonadal axis

Timing of puberty

Four of the patients were pre-pubertal at the time of diagnosis. Patient 5 who was pre-pubertal (aged 7.6 years at diagnosis) developed early puberty 2 years post-RT at the age of 9.8 years as previously described (26). A diagnosis of early puberty was made by the presence of 6 ml testes bilaterally, rapid advancement of bone age and pubertal response to a GnRH test. He was successfully treated with a GnRH analogue and attained his final target height. Patient 6 also entered puberty early developing 8 ml testes by the age of 9.8 years. He was progressing rapidly through puberty and a GnRH test confirmed a pubertal response. He was treated with a GnRH analogue to allow maximal growth and is also on target to attain his final predicted height. Patients 2 and 3, both pre-pubertal at diagnosis, had testicular volumes of 20 ml bilaterally at the ages of 14.5 and 15.5 years respectively (Table 3).

Long-term gonadotrophin concentrations and pubertal development

Patient 1, who was pubertal at diagnosis (Table 3), failed to progress through puberty with testicular volumes of 12 ml bilaterally at the age of 17.9 years. He attained testicular volumes of 25 ml at the age of 28.5 years; basal LH and FSH were 1.2 and 1.1 mU/l respectively with a serum testosterone of 6.0 nmol/l at 0900 h (adult normal range (NR) 9–9.5 nmol/l). For the remaining five patients, LH, FSH and testosterone levels were normal on long-term follow-up (Table 4).

Table 2

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Short-term GH peak (mU/l) and (time post-RT)</th>
<th>Long-term GH peak (mU/l) and (time post-RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;1.0 (2.54 years) 1.0 (2.60 years)</td>
<td>&lt;0.5 (11.3 years) 0.7 (11.3 years)</td>
</tr>
<tr>
<td>2a</td>
<td>17.9 (0.60 year)</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>16.6 (0.70 year)</td>
<td>29.7 (8.6 years)</td>
</tr>
<tr>
<td>4</td>
<td>42.9 (1.40 years)</td>
<td>50.4 (7.6 years)</td>
</tr>
<tr>
<td>5</td>
<td>65.0 (0.60 year)</td>
<td>19.2 (9.5 years)</td>
</tr>
<tr>
<td>6a</td>
<td>11.6 (0.86 year)</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Pubertal stage and testicular volume (ml)</th>
<th>Age (years)</th>
<th>Pubertal stage and testicular volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.6</td>
<td>G3 (12/10)</td>
<td>28.5</td>
<td>G3 PH4 (25/25)</td>
</tr>
<tr>
<td>2</td>
<td>6.6</td>
<td>G2 PH2 (2/2)</td>
<td>14.5</td>
<td>(20/20)</td>
</tr>
<tr>
<td>3</td>
<td>9.3</td>
<td>G3 (3/3)</td>
<td>15.5</td>
<td>G4 PH4 (20/20)</td>
</tr>
<tr>
<td>4</td>
<td>17.4</td>
<td>G4 PH3 (15/15)</td>
<td>18.8</td>
<td>G5 PH5 (20/20)</td>
</tr>
<tr>
<td>5b</td>
<td>7.6</td>
<td>G1 PH2 (2/2)</td>
<td>17.6</td>
<td>G5 PH5 (25/25)</td>
</tr>
</tbody>
</table>

G, genitalia stage; PH, pubic hair.
*Currently on GH therapy.
bGlucagon testing, all others ITT.

Prolactin

PRL levels were within the normal range in all the six patients (range 87–282 mU/l) (Table 4).

Neuropsychiatric outcome

Patient 1 was treated for depression and alcoholism in adulthood. He remains single and unemployed on follow-up. Patients 2, 4 and 6 report no cognitive problems at school/college. Patient 3 attained a higher degree and patient 5 is in full-time employment.

Posterior pituitary function

All six patients had normal electrolytes on long-term follow-up and no symptoms or signs of posterior pituitary deficiency.
Discussion

Before the development of TSS, pituitary RT was considered as possible first-line treatment for paediatric CD and a rapid response was reported when compared with the treatment in adult patients (14). The improvement of microsurgical techniques, combined with the ability to localise the pituitary adenomas by bilateral inferior petrosal sinus sampling and pituitary magnetic resonance imaging, has resulted in TSS becoming the treatment of choice (3, 27).

However, pituitary RT has been demonstrated to be effective second-line treatment for paediatric CD (11). Conventional fractionated RT appears to be more effective in paediatric patients when compared with adult CD, with cure rates quoted as 80–100% in children (11, 14, 15) as opposed to 56–83% in adults (19, 20, 22). Children are reported to respond quicker with mean time to cure of 0.8–1.0 year when compared with longer cure intervals of 1.5–4 years in adults (11, 14, 15, 20). Nevertheless, permanent hypopituitarism is a potential complication of pituitary RT in both adults and children (18, 19). In view of the small number of paediatric patients treated with external beam pituitary RT, there are few published data on long-term anterior pituitary function.

In the series of patients we report, a number of findings were demonstrated. First, following short-term GH deficiency, to which the TSS may have contributed (28, 29), recovery of GH secretion was seen in some patients. GHD is reported to be the most frequently observed pituitary hormone deficiency post-RT (2, 11, 17, 23, 30), being present in 36–68% of adults post-pituitary RT for CD, but it may be transient (19, 23). In our series, two out of six patients showed improvement of GH secretion on reassessment and another maintained normal GH secretion. It is important that children treated with pituitary RT are tested for GHD early and treated appropriately to optimise growth (29). However, transient GHD can persist after TSS for up to 5 years, hence it may be difficult to establish the relative effects of each treatment (31). Recovery of somatotroph function may occur and retesting is an important aspect of care.

Pubertal development can also be affected by pituitary RT. The disruption of pubertal development with advanced puberty was previously described (26). This was thought to be due to a defect in the hypothalamic control of gonadotrophin release or pulsatility. In the children in our series who were pre-pubertal at the time of diagnosis, puberty appeared slightly advanced with testicular volumes of 20 ml bilaterally obtained by the age of 14.5 and 15.5 years. This suggests that in the absence of overt precocious puberty, there may be subtle changes of the hypothalamic–gonadotrophin axis post-RT. In the majority of patients, PRL, thyroid, cortisol and gonadal function were normal at long-term follow-up.
One patient was unusual (patient 1). This patient was severely GHD post-TSS and subsequently developed gonadotrophin deficiency, followed by TSH deficiency and eventually ACTH deficiency. The evolution of pituitary dysfunction post-RT in adults has been well described (32). This may be due to the relative differential sensitivities of each axis to long-term radiation damage (17, 18), together with the apparent difference in the time it takes for individual anterior pituitary hormonal deficiencies to develop post-RT (20). Anterior pituitary deficiencies can appear up to 15 years post-RT (32). This evolution of anterior pituitary hormone deficiencies has also been reported in CD patients post-TSS (8). The incidence of hypopituitarism is greater in the presence of pituitary function abnormalities prior to RT, as a result of disease or TSS (18). It is well recognised that in the presence of additional pituitary hormone deficits, severe GHD is common and is likely to be persistent (23).

The long-term cognitive neuropsychological consequences of excessive hypercortisolaemia are being increasingly recognised (33, 34). At diagnosis, symptoms may arise from acute psychiatric presentations of mania and depression to more subtle features of poor concentration and hyperactivity. There is growing evidence that in adult CD patients post-TSS with or without pituitary RT, biochemical ‘cure’ of hypercortisolaemia may be associated with ongoing symptoms. Symptoms vary from failing social and interpersonal relationships, anxiety, irritability and demoralisation, to deterioration in school performance in children (7, 35, 36). The presence of depression and alcoholism together with social and interpersonal problems in one of our patients would be in keeping with this. This patient was diagnosed relatively late with a 5-year history of symptoms prior to presentation. Chronic glucocorticoid exposure also results in the apparent loss of brain volume as judged by radiological scanning. Although this appears to be reversible with the normalisation of cortisol, it remains to be seen if there is full recovery of the corresponding cognitive impairment (7, 37, 38). The general consensus is that the ‘quality of life’ following CD may be impaired despite apparent hormonal cure. The relative contribution of the disease process and treatment of this, whether this be TSS or RT, can be difficult to separate.

However, a recent study suggested that RT made little difference to the quality of life scores in this group of patients (34). Nevertheless, while overall emotional and cognitive function appeared unimpaired in the majority of our patients, this was not formally assessed.

In conclusion, this series of patients illustrates the importance of long-term follow up of paediatric CD patients treated with TSS and RT. Pituitary–gonadal function was generally maintained, allowing progression through puberty and recovery of GH secretion in some patients occurred. However, the potential cognitive neuropsychological long-term outcome in these children should not be forgotten, particularly when irradiated at a younger age.

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Received 2 October 2006
Accepted 8 January 2007

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