Long-term effects of radiotherapy for acromegaly on circulating prolactin

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Abstract. In 61 acromegalic patients, serum PRL was assessed (off medical treatment) before and 2 to 12 (mean 6.4) years after external beam radiotherapy. Before radiotherapy elevated PRL levels were present in 22 of 35 males (63%) and 12 of 26 females (46%) and were above 1000 mU/l in 11 males and 5 females. When studied for up to 5 years after radiotherapy, 22 of 23 (96%) patients who had not had surgery and who had normal PRL pre-radiotherapy showed an increased PRL level and this was also seen in 17 of 27 (63%) who had been hyperprolactinaemic initially. In contrast, 10 of 27 patients (37%) who had elevated pre-radiotherapy levels (all greater than 1000 mU/l) had a reduction in PRL values after radiotherapy. In all 11 patients who underwent surgery before radiotherapy, an increase in PRL was seen after radiotherapy. In the 21 patients followed for 10–12 years, the peak PRL value occurred 1–6 years after radiotherapy. After this, a progressive reduction of PRL to normal was seen. Normal levels were reached 4 to 10 years after radiotherapy. No correlation was found between pretreatment PRL values and final GH values in the whole group, nor between changes in PRL and the development of impaired ACTH or TSH secretion. Thus, different patterns of PRL behaviour suggest that radiotherapy treatment may either produce hyperprolactinaemia from mild hypothalamic damage or ablate PRL secreting cells if they were present in the tumour before treatment. These changes do not predict final GH results or the development of hypopituitarism after radiotherapy.

Elevated circulating prolactin is often observed in patients with acromegaly (1–5). Several mechanisms may induce this abnormality. The adenoma may contain either separate GH and PRL secreting cells (6–8), or a single cell line producing both GH and PRL (9, 10). More rarely, two distinct adenomas may be observed in the pituitary (11). The concomitant secretion of both hormones may account for the positive correlation between basal GH and PRL reported by some authors (12). Hyperprolactinaemia may also be secondary to hypothalamic-pituitary disconnection caused by pressure of the tumour mass on the pituitary stalk, with subsequent reduction of dopaminergic inhibition of PRL secretion (13, 14). Finally, hyperprolactinaemia has been documented following radiotherapy (12, 15, 16) and this has been claimed to be characteristic of patients who were normoprolactinaemic before treatment (12).

To date, two series of patients totalling 85 have been studied (12, 16). However, it is not clear whether hyperprolactinaemia is a predictive factor of a higher cure rate as has been suggested by Werner et al. (17), or whether the development of hyperprolactinaemia predicts that of hypopituitarism as a complication of external radiotherapy. Therefore we have studied 61 patients with acromegaly who underwent external beam radiotherapy between 1973 and 1985, and followed changes in serum PRL with time and correlated these with GH changes and the appearance of impaired ACTH and/or TSH secretion. The relationship between pretreatment with PRL and GH was also studied.
Patients and Methods

Sixty-one patients (35 male and 26 female, aged 23–68 years, mean 47) who were diagnosed as having acromegaly on the basis of elevated GH levels (median 65 mU/l; range 5–546) which failed to suppress after a 50 g oral glucose tolerance test were studied, and followed for between 2 and 12 years (mean 6.4). Pituitary irradiation was carried out using a 4 or 15 MeV linear accelerator to deliver a lesion dose of 4500 cGy (rads) in 25 fractions over 35 days (maximal daily dose 180 cGy). Treatment was planned individually, using the smallest target volume compatible with uniform irradiation of the lesion as detected radiologically. With immobilisation in a plastic shell, X-ray simulation and full isodosimetry, a three-field technique was employed to localise irradiation to the pituitary and minimise dose to the optic pathways, brain stem, and temporal lobes. Eleven patients, 4 male and 7 female, had previously had pituitary surgery (8 transsphenoidal and 3 transfrontal) with demonstration of positive immunostaining of cells within the tumor for GH (5 patients) or GH and PRL (2 patients). No immunostaining was available in the remaining 4 patients. An impairment in TSH (7 patients) and/or ACTH (7 patients) reserve was documented in 9 patients before radiotherapy and corrected by appropriate thyroxine and/or hydrocortisone replacement. In 46 patients treatment with bromocriptine or octreotide (somatostatin octapeptide, SMS 201-995) therapy was withdrawn 6–24 weeks before hormonal evaluation, so that no patient was receiving medical treatment aimed at reducing GH levels at the time of their assessment.

A sub-group of these patients (10 male and 11 female, aged 34–68 years, mean 50), who had all been followed for between 10 and 12 years after radiotherapy was analysed separately. No patient in this group was treated surgically.

Blood was obtained through a cannula which had been placed at 08.00 h in a forearm vein after an overnight fast and 30 min after lying at rest, at 08.30 h, for determination of serum PRL and at 08.30, 13.00, 17.00 and 19.00 h for GH. From these four values a mean serum GH was calculated (18). Thyroid and adrenal functions were also assessed by evaluating basal T₄, free T₃, index (FTI) and cortisol, as well as the serum TSH response to TRH (200 µg iv) and the cortisol response to insulin-induced hypoglycaemia (insulin tolerance test,ITT). Patients were classified as hypopituitary if given thyroxine or hydrocortisone on the basis of clinical evaluation backed up by low hormone levels. An impaired cortisol response to insulin hypoglycaemia (peak <550 nmol/l) was considered sufficient for replacement therapy.

Serum levels of GH were measured by an established radioimmunoassay standardized from 1974 against MRC 66/217, obtained from the National Institute of Biological Standards (NIBSC), Holly Hill, London. The assay employed a rabbit anti-GH antibody before 1984 when it was replaced by a sheep anti-GH antibody after an extensive study showed comparability of results.

Prolactin was measured by radioimmunoassay, standardized initially against NIBSC Research Standard A coded 71/222 (19). After 1977 the assay was standardized against the reference preparation MRC 75/504. Reagents were purchased from the North East Thames Regional Immunoassay Unit, (20) from 1979. Since 1977 PRL has been measured using rabbit anti-PRL derived from the same animal. Prior to this another ‘in-house’ rabbit anti-PRL was employed (21). Sequential calibrations have ensured that the listed normal range for serum PRL (normal values <360 mU/l, 18 µg/l) has remained unaltered for the time span encompassed by the study.

Statistical analysis was performed using paired and unpaired Student’s t-tests, analysis of variance, linear regression and the chi-squared test when appropriate. Significance was taken for p values <0.05 unless otherwise specified.

Results

Pre-radiotherapy

The mean serum PRL of the whole group was 772 ± 125 mU/l (mean ± SEM). A significant difference (p < 0.001) was found between PRL values in males (973 ± 204 mU/l) and females (505 ± 79 mU/l). Hyperprolactinaemia was present in 22 of 35 (63%) males (mean 1431 ± 286 mU/l, range 380–5000) and in 12 of 26 (46%) females (mean 817 ± 115 mU/l, range 423–1550); in 11 males and 5 females PRL levels were over 1000 mU/l. There was no correlation between PRL and GH values in the group as a whole (r = 0.143) or when males (r = 0.152) and females (r = 0.067) were considered separately (Fig. 1).

Effects of radiotherapy on serum PRL

In the whole group of patients studied 2–5 years after radiotherapy, different patterns of PRL behaviour were identified, as shown in Table 1. Previously untreated patients (Group 1) and surgically treated patients (Group 2) were separately evaluated. Group 1: In the 23 patients whose PRL was normal before radiotherapy, 22 (96%) showed an increase after radiotherapy; in the 27 patients whose PRL was raised before radiotherapy, there was a rise in 17 (63%) and a fall in 10 (37%), but this fall was only seen in patients whose pretreatment serum PRL level exceeded 1000 mU/l. Group 2: In all 11 patients, only an increase of PRL levels was observed following radiotherapy.

The individual changes in the group of 21 pa-
Patients followed for between 10 and 12 years are shown in Fig. 2. A variable increase in serum PRL levels (mean 283% of basal PRL values, range 10–1506%) was found after radiotherapy both in basally normoprolactinaemic or hyperprolactinaemic patients, no difference being observed between males and females. The peak was observed 1–6 years after radiotherapy when all but one patient (No. 4) who had previously undergone surgery with consequent hypopituitarism, were hyperprolactinaemic. A gradual reduction was then observed in most of these patients, reaching normal values 4–10 years after radiotherapy in 6 of 10 (60%) basally normoprolactinaemic patients and 3 of 11 (27%) basally hyperprolactinaemic patients.

Relationships between PRL, fall in GH and the development of hypopituitarism

No correlation was found between the pretreatment PRL value and the last GH values (Fig. 3) obtained in the 21 patients followed for 10–12 years after radiotherapy (r = 0.152). Thus a mean serum GH of under 10 mU/l was seen after radiotherapy in 6 of 10 (60%) basally normoprolactinaemic patients and in 7 of 11 (63%) basally hyperprolactinaemic patients. Furthermore, no difference in the latest GH levels was found between basally normal and hyperprolactinaemic patients. After the patients were assessed off treatment, prior medical therapy had no effect on these changes.

Two patients in this group of 21 developed an impairment in thyroid and/or adrenal function. Both patients had hyperprolactinaemia during the whole period of follow-up. None of the remaining 10 patients with normal pretreatment prolactin levels developed any abnormality in thyroid and adrenal function. When all 61 patients were considered, no differences were observed in the prevalence of ACTH and/or TSH impairment between patients who showed an increase in PRL levels 2–5 years after radiotherapy or a decrease. Impairment of ACTH and/or TSH function after radiotherapy occurred in 20 of 43 (47%) of patients who showed an increased PRL level and in 4 of 9 (44%) who had a PRL decrease. Nine patients were on replacement therapy before radiotherapy.

Discussion

In this study of acromegalic patients given external beam radiotherapy, hyperprolactinaemia was present in about half before treatment and this is simi-
Fig. 2. Serum PRL changes after radiotherapy in 21 patients followed for 10—12 years. Upper panels: elevated PRL before radiotherapy. Lower panels: normal PRL before radiotherapy. The numbers refer to the patients in Fig. 3. The dashed line portrays the upper limit of normal for PRL.

lar to reports from other authors (3—5). In contrast to other series, however (2, 12), elevated PRL levels were more common and significantly higher in male than in female patients, but no correlation between basal PRL and GH was found. This discrepancy may be explained by a different prevalence of hyperprolactinaemia due either to mixed GH and PRL secreting tumours or stalk compression. Higher PRL levels are observed in the presence of a PRL secreting adenoma, while only mild hyperprolactinaemia results from stalk compression by a non-prolactin secreting tumour (22). Our failure to find any correlation between GH and PRL levels may therefore be due to the presence in our patients of both causes of hyperprolactinaemia.

Our data show that in acromegalic patients given radiotherapy, several different patterns of changes in PRL may be found. Irrespective of basal PRL values, in previously untreated patients either an increase or a decrease in serum PRL developed, the latter being more common in the presence of basal PRL levels of greater than 1000 mU/l. In other studies of smaller series, PRL changes were less variable: Clark et al. (16) observed an increase of PRL levels in all patients irrespective of basal PRL values, while De Pablo et al. (12) showed an increase in basally normoprolactinaemic patients.
and a decrease in hyperprolactinaemic patients. Our data suggest that either hypothalamic damage with subsequent mild hyperprolactinaemia or destruction of a mixed GH and PRL secreting tumour are possible after radiotherapy; clearly a combination of these effects is possible. As it is likely that PRL levels of greater than 1000 mU/l could reflect the presence of PRL secreting tumours (22), the reduction of PRL observed in these patients after radiotherapy may reflect the effect of radiation on prolactin cells in a mixed tumour. On the other hand, the limited hypothalamic effects of radiotherapy may produce mild elevation of PRL when this was normal before treatment in patients with pure GH secreting lesions. Only rarely did PRL levels which were elevated before radiotherapy return completely to normal (3 of 11 patients). The fact that after surgery, prolactin levels rose in all patients probably represents hypothalamic damage, as in this group was included those patients with the largest tumours.

In our experience the presence of pretreatment hyperprolactinaemia does not predict the outcome of radiotherapy of acromegalic patients, since there is no relation between pretreatment PRL and latest available GH values after radiotherapy. This is in disagreement with other studies (17) but these were performed using a slightly higher dose (50 Gray) and only 7 hyperprolactinaemic patients were considered, three of whom had pretreatment GH levels <50 mU/l, a group thought to respond better and more rapidly to radiotherapy. Finally, no relationship was found between PRL levels and impairment of thyroid and adrenal function, suggesting that the hypothalamic damage inducing hyperprolactinaemia is selective and not predictive of the development of abnormalities in the secretion of other pituitary

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**Table 1.**

Serum PRL (mean ± SEM) before and 2 to 5 years after radiotherapy (RT) in 61 acromegalic patients.

<table>
<thead>
<tr>
<th>Group 1: Previously untreated, N = 50</th>
<th>Before RT</th>
<th>After RT</th>
</tr>
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<tbody>
<tr>
<td>Pre RT, PRL normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise in PRL, N = 22</td>
<td>224 ± 13</td>
<td>648 ± 76*</td>
</tr>
<tr>
<td>Fall in PRL, N = 1</td>
<td>181</td>
<td>117</td>
</tr>
<tr>
<td>Pre RT, PRL 360–1000 mU/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise in PRL, N = 13</td>
<td>540 ± 42</td>
<td>1132 ± 149*</td>
</tr>
<tr>
<td>Fall in PRL, N = 0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pre RT, PRL &gt; 1000 mU/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise in PRL, N = 4</td>
<td>1302 ± 125</td>
<td>2943 ± 1011</td>
</tr>
<tr>
<td>Fall in PRL, N = 10</td>
<td>2271 ± 488</td>
<td>1717 ± 486*</td>
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<tr>
<td>Group 2: Previously treated by surgery, N = 11</td>
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<td></td>
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<tr>
<td>Pre RT, PRL normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise in PRL, N = 4</td>
<td>185 ± 61</td>
<td>1698 ± 1311</td>
</tr>
<tr>
<td>Fall in PRL, N = 0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pre RT, PRL 360–1000 mU/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise in PRL, N = 5</td>
<td>461 ± 16</td>
<td>682 ± 68</td>
</tr>
<tr>
<td>Fall in PRL, N = 0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pre RT, PRL &gt; 1000 mU/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise in PRL, N = 2</td>
<td>1322 / 2919</td>
<td>1730 / 4705</td>
</tr>
<tr>
<td>Fall in PRL, N = 0</td>
<td>–</td>
<td>–</td>
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</table>

* p < 0.001.
hormones after radiotherapy. Our group has reported a different and lower incidence of hypopituitarism following external pituitary irradiation using an identical treatment regimen for prolactinoma (23). The reason for the difference in the development of hypopituitarism in these two groups of patients is at present unclear.

In conclusion, our data show that different patterns in PRL behaviour may be identified in acromegalic patients after radiotherapy, suggesting either the possibility of hypothalamic damage or the presence of tumourous PRL cells. Furthermore, PRL levels are not predictive of the final therapeutic result.

References

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