CLINICAL STUDY

Long term effect of external pituitary irradiation on IGF1 levels in patients with acromegaly free of adjunctive treatment

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Abstract

Objective: It is established that external pituitary irradiation (EPI) effectively reduces serum GH levels in acromegaly. However, its effect in normalising serum IGF1 has been disputed. We looked at the number of our patients who achieved persistently normal IGF1 levels whilst free of adjunctive treatment for at least 1 year after EPI.

Patients and design: We identified 63 acromegalic patients between 1964 and 2004 who received EPI. Six were excluded: three had surgery after EPI, two had no medical records available, and one had a pituitary Yttrium implant.

Measurements: Patients received 4500–5000 cGy in fractionated doses. IGF1 levels were correlated with their respective age-related reference ranges.

Results: After EPI, the number of patients with normal IGF1 and free of adjunctive medical treatment for at least 1 year were four patients by 3 years, nine patients by 5 years and seventeen by 10 years, with the current number of 25/57 (44%). Concordance between IGF1 levels and random GH dropped from 90% at the time of EPI to 65% at 3 years, 66% at 5 years and 71% at 10 years.

Conclusions: We have demonstrated that, with time, EPI achieves a normal IGF1 in significant numbers of patients with acromegaly, thus obviating the need for life-long expensive medical therapy. For each patient this benefit has to be weighed against the possibility of new hypopituitarism as a result of the treatment. Any decision to use EPI is easier in the context of pre-existent hypopituitarism.

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Introduction

External pituitary irradiation (EPI) has been used to treat acromegaly since 1909.

Professor Beclere (1) reported on its success:

“A young girl ...suffering from...gigantism was treated with crossfire through four or five areas on the fronto-temporal region. The attacks of cephalgia have disappeared ... (and there) is improvement in the visual troubles”.

Biochemical confirmation of amelioration of acromegaly after EPI was available with the development of a RIA for human GH in 1963 (2). The evidence that EPI effectively reduces serum GH levels in acromegaly is well established despite initial problems with GH assay variability (3–12).

Insulin-like growth factor 1 (IGF1) is the GH dependent peptide that mediates many of the anabolic and mitogenic actions of GH. The measurement of plasma IGF1 was proposed for the evaluation of

acromegaly in 1979 (3) but it was not until 1993 that a reliable assay became widely available. IGF1 levels are influenced by age, gender, degree of sexual maturity, pregnancy and nutritional status. Although improvements have been made to the IGF1 assay over the last 10 years, the laboratory standard issued by WHO remains sub-optimal, and there is variation between assays which may partly explain the wide range of results in the early years of the assay as outlined in Table 1.

A recent meta-analysis of the effect of IGF1 on standardised mortality ratios (SMR) showed that a normal final IGF1 was associated with an SMR of 1.1 (95% confidence interval, CI 0.9–1.4) while an elevated final IGF1 was associated with an SMR of 2.5 (95% CI 1.6–4.0). These mortality ratios were similar to GH levels with a last GH of <2.5 µg/l associated with an SMR of 1.1 (95% CI 0.9–1.4) while a last GH of >2.5 µg/l associated with an SMR of 1.9 (95% CI 1.5–2.4) (13).

The effect of EPI in normalising serum IGF1 levels has been a cause of dispute (14–25, 30) (Table 1). Barkan *et al.* reported that following radiotherapy for

Table 1 Summary of previous studies using insulin like growth factor 1 (IGF1) in the follow up of patients after external pituitary irradiation for acromegaly.

Study	No. of patients	FU mean years unless otherwise stated	Normal IGF1 at last follow up unless otherwise stated	Conventional fractionated dose range (cGy)	Adjunctive treatment withdrawal time	IGF1 assay
Ciccarelli <i>et al.</i> (1993) (21)	19	3.7	68% at 3 years	4500–5000, 1 site	1 month	RIA
Barkan <i>et al.</i> (1997) (14)	38	7	5%	4500–5040, > 1 site	2–3 weeks	Variety
Van der Lely <i>et al.</i> (1997) (22)	37	7	0%	NA	NA	NA
Thalassinou <i>et al.</i> (1998) (23)	14	Range 10–22	29%	4500–5000, 1 site	2 weeks	Direct assay
Freda <i>et al.</i> (1998) (25)	32	7.4	31%	NA	NA	RIA
Swearingen <i>et al.</i> (1998) (24)	45	8	42%	NA	NA	NA
Powell <i>et al.</i> (1999) (30)	32	6	44%	4500–5400, > 1 site	NA	Variety RIA
Biermasz <i>et al.</i> (2000) (16)	36	11	74%	2500–5000, 1 site	NA	RIA
Barrande <i>et al.</i> (2000) (17)	128	15	79%	4350–6050, > 1 site	NA	Variety RIA
Cozzi <i>et al.</i> (2001) (15)	49	Median 14, range 3–41	16% at 10 years	4000–7500, > 1 site	2 months	Variety RIA
Epaminonda <i>et al.</i> (2001) (19)	67	11	55%	4000–7500, > 1 site	1–3 months	RIA
Jenkins <i>et al.</i> (2006) (18)	884	Median 7	63% at 10 years	Median 4500, > 1 site	NA	Variety RIA

NA, not available.

acromegaly only 2 out of 38 patients (5%) taken off medical therapy for 2–3 weeks normalized IGF1 over 10 years despite attenuation of GH levels (14). However this group used more than one radiation centre, treatment technique and IGF1 assay. Cozzi *et al.* found that 8 out of 49 patients post EPI had normalized IGF1 over 10 years without the use of anti-secretory medical treatment (15). Biermasz *et al.* reported that 23/31 (74%) over 10 years had normalized IGF1 but 5 of these were on anti-secretory treatment at the time (16). Barrande *et al.* found that IGF1 levels had normalised in 81% of patients not still receiving medical treatment (30/47) at follow up of 15.4 ± 10.9 years (17). Peacey *et al.* showed in 11 patients treated with varying doses of radiotherapy that, although mean daytime GH was $< 2 \mu\text{g/l}$, IGF1 was significantly higher than in controls. They suggested the reason for the divergence between mean GH and IGF1 was that EPI caused hypothalamic damage both to the GHRH and somatostatin neuronal pathways with the result that although GH pulse amplitude was attenuated the GH trough levels remained elevated (26). Somatostatin analogues produce progressive decreases in IGF1 and GH over many months. Previous publications of the use of pituitary irradiation either provide poor documentation of this or include GH and IGF1 levels taken after adjuvant therapy has been stopped for an insufficient length of time.

We reviewed the patients at our centre who have been treated at the same radiotherapy site for the last

40 years. The aim was to determine if EPI normalised IGF1 levels consistently while free of medical treatment for at least 1 year and to look at concordance rates between IGF1 and random GH during follow up.

Materials and methods

The charts of all patients who received EPI for acromegaly between 1964 and 2004 at this centre were reviewed. Two patients had no medical records available and were excluded. Three patients had pituitary surgery undertaken after EPI. One patient had an Yttrium implant 1 year before EPI (Table 2).

All patients were diagnosed and treated at the Regional Centre for Endocrinology and Diabetes at the Royal Victoria Hospital, Belfast. The pituitary irradiation was administered at the Department of Clinical Oncology, Green Park Health Care Trust, Belfast.

Table 2 Patient characteristics.

Gender	19 F/38 M
Age at diagnosis (years)	38.1 ± 13.0
Age at EPI (years)	43.8 ± 14.9
Macroadenoma	46/57
Surgery	47/57
Multiple surgery	6
Adjunctive anti-secretory treatment pre-EPI	47/57
Hormone replacement pre-EPI	27/51
Added hormone replacement post EPI	17/51

Figure 1 Kaplan Meier graph of disease persistence over time.

Patients treated before 1977 received 4200–4500 cGy over 18–22 days. Our practice changed in 1977 when two definite and two possible cases of visual loss were encountered after irradiation treatment. Since then patients have received 4500–5000 cGy, depending on the tumour volume, in 30 fractions over 6 weeks (27).

A beam direction shell was made for each patient to ensure accuracy of treatment planning and delivery. The beam energy used was 6 MV – delivered from a linear accelerator which ensures a sharp beam edge and cut off, minimising radiation to other regions in the brain. Thermoluminescent dosimetry was used to ascertain the dose to the lens.

Follow up was carried out at our centre exclusively. The onsite Regional Endocrine Laboratory processed all samples for random clinic GH and IGF1. Serum GH concentration was assessed by various RIA assays, the latest using a double MAB technique (Delfia Kit, Wallace OY, Turku, Finland) and the intra-assay variations were <10%. IGF1 levels were available from 1992 onwards, and until 1996 samples were shipped to Charing Cross Hospital, London for an in-house assay (overall coefficient of variation (CV) <10%). Thereafter, IGF1 was measured on site by immunoassays supplied by Diagnostics Product Corporation (Los Angeles, USA) (1996–2003) and Immunodiagnostic Systems Limited (Bordon, Tyne & Wear, UK) (2003–current year; overall CV <7.5%). IGF1 results were correlated with their respective age-related reference ranges.

In many cases somatostatin analogues bromocriptine and cabergoline were used as adjunctive therapy while awaiting biochemical and clinical normalization after radiotherapy. Patients had these medications reduced and withdrawn as clinical and biochemical indices improved. IGF1 levels were taken 6–12 monthly during follow up and medical treatment restarted if levels rebounded. Random GH levels of <5 mU/l (2 µg/l) and an age- and sex-related IGF1 within the normal range were used to define concordance and were available in a subset of patients at each time point.

Statistical analysis

Data are shown as the mean $\pm$ s.d.

Results

This group ($n=57$) consisted of 19 women and 38 men. The mean age at diagnosis was 38.1 ± 13.0 years (range 14–68). Pituitary surgery was carried out in 47 patients. A macroadenoma was found in 46 patients. Six patients required more than one surgical exploration. At the time of irradiation the patients had a mean age of 43.8 ± 14.9 years (range 19–72). Adjunctive treatment pre-irradiation was initiated in 47 patients. The average duration of follow up in our clinic was 13.9 ± 9.0 years (range 2–43).

After EPI, the number of patients with persistently normal IGF1, free of adjunctive treatment for at least 1 year, were four patients by 3 years, a further five patients by 5 years, and a further eight patients by 10 years. At >10 years we identified eight more patients making a current total of 25 out of 57 patients. Disease persistence over time is illustrated as a Kaplan-Meier graph in (Figure 1).

Out of 51 patients where there was full data, 27 patients (53%) required pituitary hormone replacement before pituitary irradiation. Additional hormone replacement was required in 17 patients, of which 11 had not previously required any replacement. Three patients subsequently required GH replacement. At last follow up none of the 19 female patients were taking oestrogen replacement so this was not a confounding factor in interpreting the IGF1. Nine patients died of which three patients had normal IGF1 at last follow up.

The concordance rate between random clinic GH and IGF1 was high pre-EPI at 90% (36/40). Concordance rates subsequently dropped at 3 years after EPI to 65% (22/34). Of the discordant patients, seven patients had an elevated IGF1 and random GH <5 mU/l while five patients had a normal IGF1 but elevated random GH. The concordance rate at 5 years was 66% (19/29) and at 10 years was 71% (17/24). At 10 years five patients had an elevated IGF1 and random GH <5 mU/l while two patients had a normal IGF1 but elevated random GH.

Discussion

We undertook this study to ascertain whether EPI is effective in achieving a normal IGF1 in patients with acromegaly, without the use of continuing concomitant medical treatment, something which has been much disputed in the literature (Table 1 for summary).

The number of patients followed up in this study was comparable to, and the follow up period is longer than, many of the previous studies. In contrast to some of these, we have found that pituitary irradiation is effective in normalizing IGF1 with nearly 50% of

patients eventually being normal off adjunctive medical treatment. Radiotherapy therefore offers these patients, most with a history of failed surgery, an opportunity that they may not need life-long parenteral and relatively recently licensed treatment for acromegaly.

A recent report of the UK National Acromegaly Register Study Group has also demonstrated that significant numbers of patients have normal IGF1 levels after irradiation though in that series the length of time off adjunctive treatment was not specified (18). Our results are complimentary to these and have the advantage of being in one centre with a single laboratory, clinic and radiation site, albeit with two irradiation schedules and three IGF1 assays over the 40 years. Our centre has been able to follow up patients closely in a confined geographical area among a population with low rates of migration. By way of contrast, all our group had been free of GH or IGF1 lowering therapy for at least 1 year. We know that somatostatin analogues in particular produce progressive decreases in IGF1 and GH over many months therefore data on the length of time that adjuvant therapy has been stopped is pertinent. Previous publications either provide poor documentation of this or include GH and IGF1 levels taken after adjuvant therapy has been stopped for an insufficient length of time. As a result of these recent studies showing that EPI normalises IGF1 in a significant proportion of patients with recurrence, we tend to move to EPI in those with established hypopituitarism post-operatively and in those who, on balance, wish to attempt to avoid lifelong medical therapy at the expense of possible side-effects.

The major disadvantage of irradiation is the subsequent development of hypopituitarism. The need for this was substantial in our group. However, it should be noted that over half of the patients (27/51) were already hypopituitary prior to EPI and therefore this, the most common side-effect of EPI, was not relevant to their management. The adverse effects of EPI have been outlined in several studies (8–10, 18, 27–29). Progressive visual loss with a conventional megavoltage source has been reported by our group and others but this is exceptionally rare with modern dosage regimens and we have not seen it since our original description (27, 29). Other rare sequelae reported include brain necrosis, vascular complications and carcinogenesis.

The high level of concordance between random clinic GH and IGF1 pre-EPI (90%) reflects our policy of choosing patients with unambiguously active disease for EPI. The discordance rates subsequent to EPI (29–35%) is in keeping with the previously noted discordant rates among acromegalic patients overall (26). As yet there are no large studies in which patients with discordant results are followed for morbidity and mortality and therefore it is as yet uncertain which parameter is the best predictor. However, the drop in concordance following EPI is noteworthy and suggests that an uncoupling of the relationship between random

GH and IGF1 is real. EPI did not appear in this study to exert a much more potent effect on random GH than on IGF1 as in previous studies. It is possible that the effect of EPI on GH secretory patterns differ considerably between individual patients, possibly depending on the differential effect on somatostatin and GHRH secreting cells in the hypothalamus and GH secreting cells in the pituitary.

In summary, we have found that EPI is effective in achieving normal IGF1 in a substantial number of patients with acromegaly and this allows us to view parenteral anti-secretory therapy as a course of treatment rather than a lifelong commitment in many of these patients. The most problematic side-effect is the development of new hypopituitarism in a substantial subset. In the acromegalic group who have persistent acromegaly and hypopituitarism postoperatively we tend to move to irradiation more readily. In those free of hypopituitarism a difficult choice has to be made as to whether one embarks on lifelong medical therapy after surgery or attempts to curtail the length of this therapy by using irradiation.

It is now our clinical practice that in all patients with persistently normal IGF1 some years after EPI we attempt to reduce and stop relatively new parenteral adjunctive anti-secretory therapy while carefully monitoring GH and IGF1 levels for possible escape from control.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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