CLINICAL RESEARCH

Treatment of Cushing's disease with low dose radiation therapy

S R AHMED, S M SHALET, C G BEARDWELL, M L SUTTON

Abstract

Nineteen patients with Cushing's disease were treated with low dose external pituitary irradiation (20 Gy (2000 rad) in eight fractions over 10 days). While awaiting the effects of pituitary irradiation all patients were treated with metyrapone. Seven patients had a complete remission of their disease within six to 12 months of irradiation. They did not require any further treatment and were followed up for a mean of three and a half (range one to eight) years. Another patient had a complete remission after a second course of pituitary irradiation. A further two patients showed a significant biochemical improvement after irradiation, although they were not rendered eucorticot. There were no complications after this dose of irradiation.

These results compare favourably with those reported after pituitary irradiation at conventional doses (40-50 Gy (4000-5000 rad) over four or five weeks) but were not associated with any complications. It is therefore recommended that low dose external pituitary irradiation be used as definitive first line treatment for Cushing's disease.

Introduction

Pituitary dependent Cushing's syndrome (Cushing's disease) is the commonest form of endogenous hypercortisolism, accounting for 55-75% of reported cases of Cushing's syndrome.¹⁻³ The first successful treatment to be used in a patient with Cushing's disease was pituitary irradiation.⁴ Subsequently,

radiotherapy and bilateral adrenalectomy became the two common forms of definitive treatment for Cushing's disease.¹⁻⁶ Interstitial irradiation of the pituitary with gold-198 and yttrium-90 implants offers an alternative approach but requires a specialised technique and is successfully undertaken in very few centres.⁷ More recently there has been a vogue for selective pituitary microadenectomy,⁸⁻⁹ although cure rates vary from 25% to 100% in centres where this procedure is done routinely for Cushing's disease.¹⁰ Therefore other workers have suggested that radical surgical hypophysectomy is indicated.¹¹ For the past eight years we have been using low dose external irradiation to the pituitary and hypothalamus as initial treatment in patients with Cushing's disease. We report the results of this simple and relatively innocuous treatment.

Patients and methods

All patients with Cushing's disease seen from 1974 to 1982 at this hospital were included. Thus we studied 19 patients (17 women and two men) whose ages at the time of diagnosis ranged from 11 to 63 (median 28) years. The diagnosis of pituitary dependent Cushing's syndrome (Cushing's disease) was based on the following criteria, coupled with the clinical features of Cushing's syndrome: urinary free cortisol excretion above 290 nmol (105 µg)/24 h or 11-hydroxycorticosteroid excretion above 1050 nmol (378 µg)/24 h, or both, on two or more occasions; mild to moderately raised or "inappropriately normal" concentrations of adrenocorticotrophic hormone (ACTH); midnight plasma cortisol concentrations of over 300 nmol/l (10.9 µg/100 ml); a positive response to a standard metyrapone test³; and absence of evidence of an adrenal tumour on radioisotope or computed tomographic scanning.

Table I gives details of the investigation results. Except for one patient (case 7), who had an enlarged pituitary fossa, all the others had a normal size sella on plain radiography. Five patients (cases 6, 9, 10, 16, and 19) showed evidence of a microadenoma on computed tomography of the pituitary.

Treatment—All patients were treated with 20 Gy (2000 rad) from an 8 MV linear accelerator, delivered by a three field technique, in eight daily fractions over 10 days. At the same time all patients were started on treatment with metyrapone 1.0-2.5 g daily in four or five divided doses. The dose of metyrapone was individually tailored to achieve normal urinary free cortisol or 11-hydroxycorticosteroid excretion, or both, and plasma cortisol concentrations as near normal as possible.

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TABLE I—Age and biochemical details of patients before and after treatment

Case No	Sex	Age at treatment (years)	Before treatment						After treatment					
			ACTH (ng/l)	11-Hydroxy-corticosteroid (nmol/24 h)	Urinary free cortisol (nmol/24 h)	Plasma cortisol (nmol/l)			ACTH (ng/l)	11-Hydroxy-corticosteroid (nmol/24 h)	Urinary free cortisol (nmol/24 h)	Plasma cortisol (nmol/l)		
						Measured at:		Mean*				Measured at:		Mean*
						0900	2400					0900	2400	
1	F	21	105	1954		602	560	605	58	290		208	161	167
2	F	38	132	1810		413	371	609	38	430		450	250	213
3	F	14		1396		462	623		13	248		266	126	189
4	F	28	32	1439	430	480	348	478	23	570	150	344	179	256
5	F	53	105		400	543	548	505	86		201	314	268	333
6	F	22	62		1148	906	1300	917	30		209	542	479	449
7	M	63	633		3714	1120	1160	1198	100		124	313	306	312
8	F	27	137	1446	3180	971	664	1212	23		511	465	286	458
9	F	17	100	8490	1484	824	681	738	33		542	649	554	572
10	F	34	132	1800	1047	839	677	812	122		1606	1450	674	877
11	F	11	143	2948	1584	750	560	611	78		4000	600	700	
12	F	21		1348		580	560			2138		447	557	563
13	F	19	37	3773		781	450			872	587	535	486	486
14	F	27	50	2056		673	837	707	33	835	575	770	606	584
15	F	40	110	1482		392	665			1433		721	441	
16	F	62		1445		530	550	742		1344		577	472	598
17	F	45	105	1452		455	616	385	62	1322		333	483	508
18	F	63	118		528	637	480	567	56		417	495	336	542
19	M	33	54		1275	520	700				740	700	600	

ACTH = Adrenocorticotrophic hormone.

*Mean of five or more values estimated over 24 hours.

Conversion: SI to traditional units—11-Hydroxycorticosteroid: 1 nmol/24 h $\approx$ 0.36 μ g/24 h. Urinary free cortisol: 1 nmol/24 h $\approx$ 0.36 μ g/24 h. Plasma cortisol: 1 nmol/l $\approx$ 0.04 μ g/100 ml.

TABLE II—Median values (and ranges) of biochemical variables before and after pituitary irradiation in the seven patients who went into remission

	Normal values	Before treatment	After treatment	Significance
11-Hydroxycorticosteroid (nmol/24 h)	<1050	1624 (1396-1954)	360 (218-510)	$p < 0.01$ (n = 4)
Urinary free cortisol (nmol/24 h)	<290	770 (400-3714)	150 (122-209)	$p < 0.01$ (n = 5)
ACTH (ng/l)	<10-80	105 (32-633)	40 (23-100)	$p < 0.01$ (n = 7)
Cortisol (nmol/l):				
Measured at 2400	<250	560 (348-1300)	250 (126-479)	$p < 0.001$ (n = 7)
Mean*	200-400	607 (478-1196)	256 (167-449)	$p < 0.001$ (n = 7)

ACTH = Adrenocorticotrophic hormone.

*Mean of five or more values estimated over 24 hours.

Conversion: SI to traditional units—11-Hydroxycorticosteroid: 1 nmol/24 h $\approx$ 0.36 μ g/24 h. Urinary free cortisol: 1 nmol/24 h $\approx$ 0.36 μ g/24 h. Plasma cortisol: 1 nmol/l $\approx$ 0.04 μ g/100 ml.

Follow up and assessment—Plasma cortisol concentrations, plasma ACTH concentrations, and urinary free cortisol excretion or 11-hydroxycorticosteroid excretion, or both, were all estimated six, 12, 18, and 24 months after radiotherapy and subsequently yearly. Metyrapone was stopped four weeks before each assessment. Apart from resolution of the clinical features of Cushing's syndrome, a patient was said to be in remission when the urinary free cortisol excretion was less than 290 nmol (105 μ g)/24 h or the urinary 11-hydroxycorticosteroid excretion was less than 1050 nmol (378 μ g)/24 h, or both, on more than one occasion. Metyrapone was stopped when patients went into remission, and follow up and assessment were continued as outlined above. In those who had not achieved remission by two years after radiotherapy additional treatment was considered.

Assays and statistical methods—Plasma cortisol concentration was measured by radioimmunoassay of unextracted plasma, using sodium salicylate as a cortisol binding globulin blocking agent.¹² Urinary 11-hydroxycorticosteroids were measured by the fluorometric method of Mattingly *et al.*¹³ Urinary 17-oxogenic steroids were estimated using the Zimmermann reaction.¹⁴ Urinary free cortisol was assayed in unextracted urine at low pH by radioimmunoassay.¹⁵ Plasma ACTH was measured by radioimmunoassay.¹⁶ The significance of the results was evaluated with the Mann-Whitney U test and Wilcoxon's matched pairs signed rank test.

Results

Seven of the 19 patients (cases 1-7) were in remission six to 12 months after radiotherapy. Two patients showed improvement clinically and biochemically within one year after irradiation, with a greater than 50% reduction in urinary free cortisol excretion, plasma ACTH concentration, and mean plasma cortisol concentration; follow up of these patients continued.

Plasma ACTH concentrations in the nine patients who responded to radiotherapy showed a significant ($p < 0.01$) reduction, from a median before treatment of 105 (range 32-633) ng/l to a median of 40

FIG 1—Adrenocorticotrophic hormone (ACTH) concentrations before and after radiation therapy in eight of the nine patients who responded. In the ninth patient only a value after treatment was available.

(range 23-100) ng/l (fig 1). One patient (case 7) had a high ACTH concentration of 633 ng/l, well above the usual range seen in patients with Cushing's disease.¹⁷ However, the pituitary fossa was enlarged with evidence of an adenoma and there was no evidence of tumour elsewhere to suggest an ectopic source of ACTH. He had a remission

within six months after radiotherapy, confirming that his disease was pituitary dependent. The median urinary free cortisol and 11-hydroxycorticosteroid excretions before treatment among the seven patients who were cured were 770 nmol (279 μ g)/24 h (range 400-3714 nmol (145-1346 μ g)/24 h; n=4) and 1624 nmol (585 μ g)/24 h (range 1396-1954 nmol (503-703 μ g)/24 h; n=4) respectively; after remission median values were within the normal range, being 150 nmol (54 μ g)/24 h (range 122-209 nmol (44-76 μ g)/l; n=5) and 339 nmol (122 μ g)/24 h (range 290-570 nmol (104-205 μ g)/24 h; n=4) respectively (table II). Though normal diurnal variation of plasma cortisol concentrations was restored in only three of the seven patients, the midnight plasma cortisol concentrations showed a significant ($p < 0.01$) reduction (fig 2). The mean plasma cortisol concentration (mean of five or more values estimated over 24 hours) in six of the

FIG 2—Cortisol concentrations measured at 2400 and as a mean of five or more values obtained over 24 hours before and after radiotherapy in eight of the nine patients who responded. In the ninth patient only a mean concentration after treatment was available.

Conversion: SI to traditional units—Cortisol: 1 nmol/l $\approx$ 0.04 μ g/100 ml.

seven patients was reduced significantly ($p < 0.01$) to an acceptable mean of 245 nmol/l (8.9 μ g/100 ml) (range 167-333 nmol/l (6.1-12.1 μ g/100 ml). There was no significant difference in the severity of Cushing's disease between the responders and non-responders as judged by urinary free cortisol excretion, 11-hydroxycorticosteroid excretion, midnight plasma cortisol concentrations, and mean plasma cortisol concentrations.

Full assessment of anterior pituitary function was carried out in all 19 patients after radiotherapy. There was no evidence of hypothyroidism, gonadotrophin deficiency, or hyperprolactinaemia after one and a half to nine (mean 3.6) years of follow up. All responders showed a normal growth hormone response to an insulin tolerance test. We could not assess the effects of radiation on the growth hormone state of the non-responders as Cushing's disease per se may be associated with blunted growth hormone responses to pharmacological stimuli. Regular menstrual cycles resumed within six to 12 months after radiotherapy in four of the five premenopausal women who had previously been amenorrhoeic. Three of these women subsequently had normal pregnancies.

Of the 12 patients who did not have a remission after radiotherapy, two showed improvement as defined above and continued to take metyrapone, five had bilateral adrenalectomy, three received long term medical treatment with metyrapone, and one had a total hypophy-

sectomy. The final patient received a second course of low dose pituitary irradiation and went into remission within the next six months.

Discussion

Since Harvey Cushing first treated one of his patients with pituitary irradiation,⁴ radiotherapy has been widely used as a definitive treatment for Cushing's disease. Generally, conventional pituitary irradiation for Cushing's disease has been with 38.0-52.5 Gy (3800-5250 rad) delivered over 31-52 days.^{1 5 18 19} Orth and Liddle reported cures in 23% and improvement in 29% of 44 patients who were treated with 40-50 Gy (4000-5000 rad) over about a month and followed up for one to 14 years (mean nine), with no recurrences.¹ Jeffcoate *et al* observed a cure in only one of eight patients treated with 45 Gy (4500 rad).²⁰ Dohan *et al* obtained a response in 41% of their patients treated with 38.0-52.5 Gy (3800-5250 rad) over 31-52 days,⁵ and Soffer *et al* in 50% of patients treated with 38-40 Gy (3800-4000 rad) over 39-52 days.¹⁸ High dose external irradiation as used above has caused blindness,²¹ and in patients treated similarly for acromegaly causes hormonal deficiency.²² We have also observed the progressive development of pituitary hormonal deficiency after treatment with 35-40 Gy (3500-4000 rad) for pituitary tumours.²³ We have not, however, come across any cases of hypopituitarism in over 50 patients treated with 20 Gy (2000 rad) in eight fractions over 11 days.²³ Patients with acromegaly have been successfully treated with low doses of 21-30 Gy (2100-3000 rad) and, similarly, patients with Cushing's disease have responded to treatment with 15-28 Gy (1500-2800 rad).²⁴ If remission rates achieved in Cushing's disease with low doses of radiation are equivalent to those achieved with conventional doses then low dose treatment would seem preferable. Besides having the radiobiological advantage of a lower dose to normal brain tissue, this dose is not associated with development of hypopituitarism and has the advantage of a shorter course of treatment.

We obtained remission in seven of our 19 patients with Cushing's disease treated with low dose irradiation (20 Gy (2000 rad) in eight fractions over 10 days). Remission occurred within six to 12 months after radiotherapy. After a mean follow up of three and a half years (range one to eight) all seven were still in remission and did not require any further treatment. In four of the five premenopausal women who had previously been amenorrhoeic regular menses were re-established within one year of radiotherapy and three of them had a normal pregnancy subsequently.

Two patients showed improvement after radiotherapy but still had hypercortisolism one year after treatment and were being controlled with metyrapone. Our usual policy is to allow up to two years for a remission to occur before proceeding to adrenalectomy, except in cases where there are overriding indications for earlier intervention. These two patients may still go into remission as cures have been observed as late as one and a half to three years after radiotherapy.^{19 20} One of our patients who did not respond to radiotherapy initially was given a second course of low dose pituitary irradiation two years later. She had a remission within six months after the second treatment. Therefore it is reasonable to state that 42% (eight) of our 19 patients had a remission after radiotherapy and 11% (two) showed improvement. Our results compare favourably with the figures of Orth and Liddle of 23% and 29% (cure and improvement, respectively) and with the 50% cure rate achieved by Soffer *et al* with conventional doses of radiotherapy.^{1 18}

There was no difference in the severity of the disease, as judged by biochemical criteria, between responders and non-responders, suggesting that low dose radiation treatment is equally effective in patients with mild and severe disease. There was also no significant difference between the ages of the responders and non-responders. Jennings *et al* reported higher cure rates of 78% in younger patients (below 20 years of age)

with conventional radiotherapy.¹⁹ Only four of our 19 patients, however, were younger than 20 years of age when irradiated.

The development of Nelson's syndrome is the most serious complication of bilateral adrenalectomy, and two recent series reported incidences of 29% and 28%.^{25 26} Though conventional radiotherapy does not prevent the development of Nelson's syndrome,²⁷ it does seem to reduce its incidence.²⁸ Whether low dose radiation treatment will exert a similar beneficial effect in patients who subsequently require adrenalectomy is not known. Five of our patients had an adrenalectomy and were followed up for two to eight years with no evidence of Nelson's syndrome.

In conclusion, we recommend that patients with Cushing's disease be offered initial treatment with low dose radiation treatment, especially in centres where neurosurgical skill in microadenomectomy is not readily available. Those patients who do not have remission of their disease by one year after radiotherapy should be considered for bilateral adrenalectomy. We believe that by this approach at least one third of patients with Cushing's disease have a chance of cure with a relatively simple and non-invasive treatment, which in our experience does not have any complications.

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Lymphadenopathy and selective IgA deficiency

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Abstract

Four men presented with unexplained lymphadenopathy. Three had a history of recurrent respiratory infections for several years, and two had lymph node or hepatic granulomas. None was noted to have symptoms of immunodeficiency at the time of presentation.

In one patient routine direct immunofluorescence study failed to detect IgA, and immunological investigations were therefore conducted in the rest. In all patients the findings were similar and characterised by a severe deficiency of IgA.

In the absence of a more serious cause selective IgA

deficiency may be enough to explain "idiopathic" lymphadenopathy.

Introduction

Lymphadenopathy is a common clinical problem with a multitude of causes including, on rare occasions, immunodeficiency syndromes. Although it is a recognised feature of common variable hypogammaglobulinaemia in a minority of patients,¹ lymphadenopathy has not been associated with selective IgA deficiency. The four cases reported here suggest that it may not only be associated with IgA deficiency but may be a presenting feature.

Case histories

CASE 1

A 29 year old man had been investigated on three occasions over five years because of recurrent axillary lymphadenopathy and nocturnal sweating. On each occasion lymph node biopsy had shown follicular hyperplasia and granulomas without evidence of mycobacterial or fungal infection. Thrombocytopenia had also been present, which

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