Occasional Review

Successful treatment of Cushing's disease using yttrium-90 rods

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Abstract

Interstitial irradiation using yttrium-90 (^{90}Y) rods implanted by needle into the pituitary gland was used as primary treatment in 16 patients with pituitary dependent Cushing's disease. Clinical and biochemical remission was observed within three to six months in 13 and in the remaining three after a supplementary implant. There was no perioperative morbidity. Follow-up from the time of definitive operation ranged from six to 123 months (mean 39). No recurrence has been observed. The return of a normal diurnal cortisol rhythm has been observed in 10/12 patients studied after remission. Some form of long-term pituitary hormone replacement therapy was required in only the six patients who had received the largest irradiation dose. Implantation of ^{90}Y is safe and effective treatment for patients with Cushing's disease, comparing favourably with selective trans-sphenoidal pituitary surgery.

Introduction

As most patients with Cushing's disease (pituitary dependent adrenocorticotrophic hormone hypersecretion associated with bilateral adrenocortical hyperplasia) have an underlying pituitary adenoma,[1-4] therapeutic measures should logically be aimed directly at the pituitary. Conventional external irradiation (deep *x*-ray) to the pituitary fossa has been widely used, but, except for children,[5] has been shown to be generally ineffective, with a remission rate of less than 20%.[6] Remissions are not only unpredictable after deep *x*-ray treatment, they may take several months, or even years, to develop, so that additional treatment with drugs is needed to decrease adrenocortical hyperfunction in the interval. The most widely used drug, metyrapone, requires careful monitoring by a specialised endocrine unit, may exacerbate hirsutism, distressing for women,[7] and is expensive.

Other irradiation techniques used include heavy-particle treatment in the United States[8] and our own past experience with interstitial irradiation[9] using yttrium or gold. Both approaches have been much more successful than conventional deep *x*-ray treatment (with each reporting a greater than 60% remission rate), but hypopituitarism has been a common long-term complication. The same problem arises after attempts to remove the tumour completely by total hypophysectomy.[10] In recent years selective surgical removal of adrenocorticotrophic hormone-secreting pituitary tumours by the trans-sphenoidal route[11] has become popular[12,13] because of encouraging results both in terms of initial remission (75%-94%)[1-4] and maintenance of normal pituitary function. We have therefore analysed our experience over the past decade using interstitial irradiation with ^{90}Y to assess whether it still has an important role in managing Cushing's disease.

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Patients and methods (table)

Between May 1971 and March 1980, we treated 17 patients (4 men, 13 women) with a diagnosis of pituitary dependent Cushing's disease with interstitial irradiation using ^{90}Y as primary pituitary treatment, and this series is consecutive to our initial report using the technique.[9] Clinical and biochemical follow-up has been possible in all but one man who returned abroad two weeks after an uneventful implantation. The ages of the remaining 16 patients at referral ranged from 12 to 54 (mean 33·8) and the duration of history from one to 10 years (mean 3·4).

The diagnosis was based in 15 patients on all of the following biochemical criteria: (1) persistently raised concentrations of urinary free cortisol; (2) abnormally raised midnight serum cortisol concentrations; (3) detectable concentrations of plasma adrenocorticotrophic hormone (in the 13 in whom this hormone was measured); (4) a fall in urinary free cortisol or urine 17-oxogenic steroids, or both, by at least half the basal value after taking dexamethasone (2 mg 8-hourly for three days); and (5) a rise in 17-oxogenic steroids or plasma 11-deoxycortisol (compound S), or both, to more than double basal values after taking metyrapone (750 mg 4-hourly for 24 h). In the remaining patient (case 13), who had cyclical Cushing's syndrome, a pituitary cause was suspected from repeated studies over several years but results of her individual tests did not always meet with the above criteria.

Radiological studies included coned views of the pituitary fossa and hypocycloidal lateral tomography. Twelve patients had a normal pituitary fossa and four an abnormally shaped or enlarged fossa suggestive of an intrasellar tumour. An air encephalogram performed in the patient with the largest sella (case 15) showed no evidence of suprasellar extension.

PITUITARY IMPLANTATION

The technique for implantation and the planning of dosimetry has been described.[14] Interstitial irradiation was applied using a pair of ^{90}Y seeds implanted under general anaesthesia and biplane *x*-ray fluoroscopy control. The whole procedure was usually completed within one hour.

Twelve patients with a normal pituitary fossa were given a dose of irradiation designed to deliver 20-50 kilorads at the periphery of the fossa, and the four with an abnormal fossa 150 kilorads. Three patients subsequently requiring a supplementary implant were given 150 kilorads at the gland periphery.

HISTOLOGY

A biopsy specimen adequate for histological examination was obtained in six patients, and in all a pituitary tumour was identified. Immunocytochemical staining undertaken in four showed that all were adrenocorticotrophic hormone-containing tumours.

POSTIMPLANTATION ASSESSMENT

Discharge from hospital was usually two weeks after operation. The first inpatient follow-up was arranged from three to six months later, and generally on an annual basis thereafter. Endocrine assessment included measurements of urinary free cortisol, 9 am and 12 midnight serum cortisol, serum thyroxine and tri-iodothyronine and prolactin concentrations, and gonadal steroids. A combined pituitary function test was also usually undertaken.[15]

HORMONE MEASUREMENTS

Urinary free cortisol and serum cortisol concentrations were measured by a competitive binding protein assay,[16] oxogenic steroids by the method of Appleby *et al*,[17] and other hormones by established radioimmunoassay techniques.

Results

INITIAL CLINICAL AND BIOCHEMICAL FOLLOW-UP

At the first reassessment, clinical improvement was apparent in 14 patients. Biochemical remission, as judged by normal 24-h urinary free cortisol concentrations or the development of clinical dependence on corticosteroids in the interval was found in 13. In three with persistently raised urinary free cortisol concentrations, a supplementary implant was administered between nine and 20 months after the first, and all subsequently achieved a clinical and biochemical remission within three months.

A reduction in facial plethora, muscle weakness, and the disappearance of psychiatric symptoms were prominent early clinical signs of remission. Objective changes included a mean ($\pm$SEM) fall in both systolic and diastolic blood pressure of 23 ± 5 mm Hg and 17 ± 3 mm Hg respectively, and a mean weight loss of $5{\cdot}0\pm1{\cdot}6$ kg. Abnormal glucose tolerance was normalised or improved in six of the seven patients reassessed, and no patient still required insulin. After implantation, nine patients needed corticosteroid replacement therapy, of whom six had only a temporary need (usually for four to five months). Two needed desmopressin because of diabetes insipidus, but one for only a week after implant.

No perioperative morbidity was associated with the implant procedure, and in particular no episodes of infection or cerebrospinal fluid rhinorrhoea.

LONG-TERM FOLLOW-UP (table)

Long-term follow-up ranged from 6 to 123 months (mean 39) from the time of the definitive implantation procedure. At the last follow-up, all patients had urinary free cortisol excretion rates within the normal range, apart from the three who are still clinically dependent on corticosteroids. Of 12 non-corticosteroid-dependent patients studied both before and after operation, a diurnal cortisol rhythm, with values within our laboratory reference range, has returned in 10. Some form of permanent pituitary hormone replacement therapy has been needed in six patients, all of whom had at least 150 kilorads irradiation, and the three who required a supplementary implant. Three have needed replacement corticosteroids, of whom two also required sex steroids, one also thyroxine, and one desmopressin because of persistent diabetes insipidus. Two other patients have required only thyroxine, which became evident at 12 and 54 months post-implant respectively, and the sixth patient needed sex steroids.

Normal gonadal function, judged in men by restored potency and normal testosterone values, and in premenopausal women by a regular menstrual cycle with normal plasma oestradiol, was maintained in all three men, and in five of the eight premenopausal women, including one (case 2) who has had two full-term pregnancies two and five years after her implant procedure.

An impaired gonadotrophin response to luteinising hormone-releasing hormone (100 μg) was shown in two of three premenopausal women (cases 12 and 15) with persistent amenorrhoea post-implantation. Both had received at least 150 kilorads of interstitial irradiation. Gonadotrophin responses after the releasing hormone remain normal in the other premenopausal women tested.

Marginally but inappropriately raised serum prolactin concentrations were found in two patients at last follow-up, both of whom were normoprolactinaemic before implant (cases 11 and 16).

The thyroid-stimulating hormone response to thyrotrophin-releasing hormone (200 μg) remains normal in nine of the 10 patients tested and not requiring thyroxine, and slightly reduced in one (case 7).

Discussion

All patients treated with ^{90}Y for Cushing's disease achieved a clinical and biochemical remission without postoperative morbidity and in none has there been evidence of recurrence at last follow-up. While excellent initial remission rates have been reported using selective transsphenoidal hypophysectomy,[1-4] recurrent disease has been observed in all but one large series and, in this latter study,[1] follow-up was limited in all cases to under three years. With long-term surgical follow-up studies it would not be a surprise if the recurrence rate increased with time since histological evidence suggests that tumour cells are often left behind in the pituitary after selective adenomectomy operations.[18] It is not possible to predict in which patients recurrence may occur, but the return of a normal diurnal rhythm for cortisol may be an important parameter of cure. After ^{90}Y implantation this was observed and maintained in 10 of 12

Clinical and biochemical data before and after ^{90}Y implantation for 16 patients with Cushing's disease

Case No	Sex	Age (y) at time of implant	Duration (y) of history	^{90}Y dose kilorads	UFC nmol/24 h¶ (normal range <270)		Serum cortisol nmol/l (normal 0900 h value <500 nmol/l) (normal 2400 h value <200 nmol/l)				Duration of follow-up (months)§	Long-term replacement treatment
					Before implant	At last follow-up	Before implant		After remission			
1	F	12	2	20	675	92	675	797	386	107	78	Nil
2	F	21	2	20*	490	110	459	527	189	68	123	Nil
3	F	52	6	20*	726	83	554	554	233	<30	93	Nil
4	F	54	2	150†	355	152	581	413	521	289	45	Nil
5	M	18	5	20	953	43	1281	599	140	45	28	Nil
6	M	35	2	150†	484	236	323	335	207	43	45	Thyroxine
7	F	36	6	20+150‡	483	on steroids	454	358	on steroids		12	Corticosteroids, sex steroids
8	F	34	2	150*†	2856	74	1053	1048	276	108	54	Thyroxine
9	F	32	2	50	1089	95	756	430	459	—	22	Nil
10	F	17	2	50	1242	107	571	628	193	<30	47	Nil
11	M	14	2	20	172	194	557	679	209	<35	25	Nil
12	F	32	3	50+150*‡	583	263	—	—	292	127	12	Sex steroids
13	F	45	10	20	249‖	68	576	450	230	<50	12	Nil
14	F	54	1	50+150‡	511	on steroids	1314	256	on steroids		6	Corticosteroids, thyroxine
15	F	31	3	150*†	532	on steroids	400	538	on steroids		13	Corticosteroids, thyroxine, desmopressin
16	F	53	2	50	1184	222	729	533	275	285	16	Nil

*Pituitary tumour shown on biopsy.
†Expanding pituitary tumour suspected on x-ray examination.
‡Implantation patients who required a supplementary implant.
§Last biochemical assessment since definitive implant.
‖Patient with cyclical Cushing's disease.
¶Values are means of at least two samples.

patients studied, while in two surgical series reporting similar data the figures were six out of seven and five out of nine patients respectively.[3 4] While the absence of a normal diurnal rhythm in two implanted patients suggests that their tumour has been incompletely destroyed, they remain clinically well and have normal 24-h urinary free cortisol secretion rates. We suppose that the remaining tumour mass is insufficient to induce hypercortisolism and that the effect of interstitial irradiation is protective against further tumour growth. Of 20 patients in our initial series[9] who obtained a remission with ^{90}Y only, none has relapsed in the subsequent 10 years of follow-up.

Maintenance of normal pituitary function is also important in assessing the overall efficacy of treatment. A third of our patients have required some form of permanent replacement treatment after implantation, but were only those receiving the highest irradiation doses. This proportion is considerably less than that observed after total hypophysectomy[10] but is higher than that reported after selective adenomectomy.[1 3 4] Nevertheless, gonadal function was preserved in all men and most premenopausal women. We have previously shown a pronounced improvement in the gonadotrophin response to the releasing hormone (LHRH) in women with Cushing's disease going into remission after implantation.[19] The same finding also applies to all premenopausal women in the present series not receiving the highest irradiation doses, and had been maintained at last follow-up.

This series shows a considerable improvement in remission rate and reduction in hypopituitarism compared with our initial report published almost a decade ago[9] for several reasons. Firstly, our experience indicated that the higher local intrapituitary dose of irradiation obtained using the β-emitter ^{90}Y was more successful in inducing and then maintaining a remission than that obtained using the lower but more wide-ranging dose of irradiation from the γ-emitter ^{198}Au. Secondly, experience had shown that if a tumour was large enough to deform the sella, a high dose of irradiation was essential, and this policy has been applied in the current series. Thirdly, no patients in this series presented with evidence of extrasellar tumour invasion, a condition in which interstitial irradiation is unlikely to be curative.[9] Surgery may similarly be unsuccessful in such cases.[3 11] Finally, the lack of any perioperative complications may relate to increased experience with the technique.

In conclusion, our results indicate that interstitial irradiation with ^{90}Y is valuable for patients with Cushing's disease and compares favourably with the best results obtained after selective transsphenoidal hypophysectomy. Remission after a single therapeutic intervention in patients with a normal pituitary fossa at presentation has not as yet been associated with the need for long-term replacement therapy for up to a period of 10 years of follow-up. In patients who are seen with an already enlarged pituitary fossa, however, the increased dose of irradiation administered, while able to effect a complete cure, is likely to result in the need for some form of long-term pituitary replacement. This is also true for patients without an enlarged fossa requiring a second implant. In this latter group the initial failure of remission may have been due to positioning of the implant seeds in the centre of the pituitary gland when anatomically the tumour was laterally situated.[4] The use of pituitary examination by computed tomography should in future enable more accurate localisation of a tumour within the fossa, and prevent the need for a supplementary implant.

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Is there any evidence that visual display units have a deleterious effect on the skin of the face? If so what preventive measures are advised?

There have been several claims that visual display units may produce symptoms in the skin of operators. The evidence is far from firm, however, and such experimental studies that have been performed have not come up with any ideas about underlying aetiology. The possibilities are that it is: (*a*) a radiative effect of the "optical radiation" emitted by the screen; (*b*) somehow due to static electricity associated with the unit; (*c*) of psychological origin. The first option seems most unlikely for Cox (in a paper given at a conference at Loughborough University, 1980) and many others have made extensive radiation measurements on visual display units, and no hazard can be detected. The static charge around a visual display unit may be relatively high, but hardly anything is known about how to connect this convincingly with skin symptoms. The suspicion that psychological causes may be important rests on the surmise that the sufferers have nearly all been young women, possibly bored with their job. (For details see the paper by Nilsen,[1] who gives full references, and a letter by Linden and Rolfsen,[2] who attempt to make a case for blaming static electricity.) Whatever its cause, if this condition is real visual display unit occupational dermatitis seems to be rare, and it is not possible to suggest any preventive measures.—I A MAGNUS, professor of photobiology, London.

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