PAPERS AND ORIGINALS

Treatment of Nelson's syndrome by pituitary implantation of yttrium-90 or gold-198

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Summary

Eight patients with Nelson's syndrome were treated with a pituitary implant of yttrium-90 or gold-198 four to 16 years after adrenal surgery. All had considerable pigmentation. One already had cranial nerve abnormalities and visual field defects and had had both a craniotomy and deep x-ray treatment. Radiographs showed that the pituitary fossa was abnormal in seven patients. A biopsy performed in six cases showed mucoid (or basophil) adenoma in all. In the four specimens examined ACTH was identified by electron microscopy or immunofluorescence, or both. Patients were followed up after pituitary implantation for three months to 12 years. All showed decreased pigmentation, and six became normal. Four patients regained normal ACTH levels and the other two studied had decreased levels. In no case did new cranial nerve disease or further sellar expansion develop since operation, and two patients showed remodelling of the sella. Complications were temporary leakage of cerebrospinal fluid and diabetes insipidus in one patient and gonadotrophin deficiency in another.

Introduction

In 1958 Nelson reported a patient who developed an ACTH-producing tumour of the pituitary gland after bilateral adrenal-

ectomy for Cushing's disease.¹ After the initial report Nelson described a further nine patients,² and the syndrome now bears his name. These tumours are apt to be unusually aggressive, undergoing rapid expansion with compression and even invasion of suprasellar and parasellar structures.^{3,4} Surgical removal of the tumour, deep x-ray or heavy particle treatment, and a combination of these procedures have met with variable success. We describe here our experience with eight patients with Nelson's syndrome who were treated with a pituitary implant of ⁹⁰Y or ¹⁹⁸Au or a combination of both.

Patients and methods

Nelson's syndrome was defined as gross pigmentation with or without a radiologically evident pituitary tumour, developing after previous effective adrenalectomy and despite adequate replacement therapy. Three patients (cases JR, WC, MR) have been briefly referred to.⁵

Clinical data at the time of adrenalectomy for Cushing's disease are summarised in table I. Three patients with initial partial adrenalectomy had the remnant of the adrenal gland removed because of recurrence of Cushing's disease. Histology of the adrenal gland showed adrenal hyperplasia in all cases. Radiographs of the pituitary fossa at the time of adrenalectomy were available for only four patients: one had an abnormal, one a doubtfully abnormal, and two a normal fossa.

TABLE I—Clinical details at time of adrenalectomy

Case No	Age	Sex	Type of adrenalectomy	Radiographs of pituitary fossa at time of adrenalectomy
1	42	F	Total	Normal*
2	35	F	Total	
3	29	F	One total and one subtotal, remnant removed 3 years later	
4	47	F	Unilateral	Normal Doubtfully abnormal Abnormal
5	19	F	Total	
6	25	M	One total and one subtotal	
7	23	M	One total and one subtotal, remnant removed 3 years later	
8	12	M	One total and one subtotal, remnant removed 2 years later	

*Examination made one year after last adrenalectomy.

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TABLE II—Clinical details at time Nelson's syndrome was diagnosed

Case No	Age at diagnosis of Nelson's syndrome	Years after last adrenalectomy	Replacement dose of steroids	Clinical features	Radiographs of pituitary fossa at time of implantation
1	44	2	Hydrocortisone 30 mg/day, fludrocortisone 0.1 mg alternate days	Pigmentation only	Abnormal
2	38	3	Cortisone acetate 37.5 mg/day, fludrocortisone 0.1 mg/day	Pigmentation only	Abnormal
3	39	7	Dexamethasone 0.3 mg/day, fludrocortisone 0.1 mg/day	Pigmentation only	Abnormal
4	54	7	No adrenocortical insufficiency, not on replacement therapy	Pigmentation only	Normal
5	25	6	Hydrocortisone 40 mg/day	Pigmentation only	Abnormal
6	29	4	Cortisone 37.5 mg/day	Pigmentation only	Abnormal
7	26	3	Cortisone 50 mg/day	Partial lesion of left 3rd and 4th cranial nerves, small bitemporal field defect, pigmentation	Abnormal
8	28	14	Cortisone 37.5 mg/day, fludrocortisone 0.2 mg/day	Pigmentation only	Abnormal

TABLE III—Details of pituitary implant, complications, and pituitary function after implant

Case No	Date	Pituitary implant		Pituitary function at last assessment		
		Dose (rads at gland surface)	Complications	LH-RH test	TRH test	Other
1	28 Feb 1975	⁹⁰ Y 150 000 rads	Transient 3rd cranial nerve paresis	Normal	Normal	
2	5 July 1974	¹⁹⁸ Au 10 000 rads	Nil	Normal	Normal	Normal GH response
3	8 Nov, 1968	⁹⁰ Y 50 000 rads	Nil	Normal	Normal	
4	1 Feb, 1963	¹⁹⁸ Au } 10 000 rads ⁹⁰ Y }	Nil	Normal	Normal	
5	23 Feb, 1973	⁹⁰ Y 50 000 rads	Nil	Normal	Started on thyroxine elsewhere	Diabetes insipidus
6	9 April, 1965	⁹⁰ Y 50 000 rads	CSF leak (successfully plugged)			
7	1 Dec, 1972	⁹⁰ Y 50 000 rads	Nil	On androgens before implant	On thyroxine before implant	
8	18 Jan, 1974	⁹⁰ Y 150 000 rads	Nil	Low basal LH before pituitary implant, now on HCG	Normal	
	9 June, 1972	⁹⁰ Y 50 000 rads	Nil			

LHRH = Luteinising hormone-releasing hormone. HCG = Human chorionic gonadotrophin. GH = Growth hormone.

Clinical data when Nelson's syndrome was diagnosed are shown in table II. The mean age at diagnosis was 35 years, and a mean of six years had elapsed after the last adrenal surgery. At the time of diagnosis all but one (case 4) of the patients were on full replacement treatment. All showed considerable pigmentation. One patient (case 7) had a partial lesion of the 3rd and 4th cranial nerves and a small bitemporal field defect; 14 years before seeing us for pituitary implantation he had had a craniotomy to remove the pituitary tumour and then external deep x-ray treatment. No other patient had received any previous treatment to the pituitary gland. Radiographs at the time of implantation showed an abnormal pituitary fossa in seven patients. In case 4 the pituitary fossa was normal at the time of adrenalectomy and remained unchanged when the patient was treated for Nelson's syndrome eight years later. In cases 3 and 5 the fossa enlarged in the period between adrenalectomy and diagnosis of Nelson's syndrome (seven and six years respectively).

Radiology—Coned views of the pituitary fossa and lateral hyocycloidal tomography of the sella were carried out in all patients at the time of pituitary implantation. Sellar x-ray pictures were classified as abnormal, doubtfully abnormal, or normal. Air encephalograms were also made in four patients (cases 5, 6, 7, and 8). None showed significant suprasellar extension or extension of the subarachnoid space into the pituitary fossa.

Pituitary implants—The operative technique and planning of dosimetry have already been described.⁶ The irradiation doses quoted here (table III) were the planned doses at the gland surface. Five patients were implanted with ⁹⁰Y 50 000 rads and one of these (case 7) was re-implanted with ⁹⁰Y 150 000 rads as his pigmentation had decreased only slightly and his plasma ACTH levels remained abnormally high. One patient was implanted with ⁹⁰Y 150 000 rads, one with ¹⁹⁸Au 10 000 rads, and one with a combination of ¹⁹⁸Au and ⁹⁰Y to give 10 000 rads to the gland periphery. The pituitary implants were carried out four to 16 years (mean eight years) after the patients' last adrenal surgery.

Plasma ACTH—Plasma ACTH was assayed by radioimmunoassay.⁷ The normal range at 9 am is <10–80 ng/l.

Histology—The biopsy samples were processed as described.⁸ Immunostaining was carried out on formalin-fixed paraffin sections by the Coons's indirect technique.⁹ Rabbit antiserum to human ACTH (Wellcome) was used as the first layer and fluorescein-conjugated

goat anti-rabbit globulin (Hyland) as the second layer. Controls for immunostaining included the use of antihuman growth hormone, antihuman chorionic gonadotrophin (Wellcome), and non-immune rabbit serum as the first layer. The sera were diluted 1 in 10 with 0.01 M phosphate-buffered normal saline, pH 7.0.

Follow-up after pituitary implant—We usually re-admit patients for reassessment three months and one year after pituitary implantation and thereafter see them each year, unless they need more frequent follow-up. The mean period of follow-up in this series was five years (range three months to 13 years). One patient (case 6) died from an unrelated cause three years after his pituitary implant, and another (case 5) became an inpatient elsewhere because of another condition, so we had no follow-up information since the second year after her implant. At recent reassessments the patients had plasma ACTH assayed at 9.00 am and at midnight on two successive days, and on one of these days plasma ACTH was also assayed 60 and 120 minutes after their usual morning dose of corticosteroid. General pituitary function was tested by the combined pituitary function test,¹⁰ using gonadotrophin releasing hormone and thyrotrophin releasing hormone, and in some cases the insulin tolerance test.

Results

Pigmentation—In six patients skin pigmentation became normal; one patient (case 4) remained normally pigmented 13 years after implantation. There was almost complete loss of pigmentation in case 3 but only slight reduction in deep pigmentation in case 7.

Tumour growth—No patient developed new cranial nerve disease since implantation, and no patient showed further expansion of the pituitary fossa. After implantation a small reduction in the size of the sella was noted in case 5 after six months, and slight reossification of dorsum and lamina dura occurred in case 3 three years after. The other patients showed no significant change. In one patient (case 6) post-implant x-ray films were not available for comparison.

Plasma ACTH—The pre- and post-implant plasma ACTH levels are shown in table IV. Pre-implant plasma ACTH levels were grossly raised in all five patients assessed, and it is interesting to note that the levels fell sharply after the usual morning maintenance dose of steroid, although not into the normal range. At follow-up four patients (cases

1, 2, 4, and 5) had normal plasma levels and were all normally pigmented. In case 8 the levels fell substantially but were still abnormal; nevertheless, he was no longer pigmented. Case 7, who before implant had the highest plasma ACTH levels (and the largest tumour), still had very high plasma ACTH levels, although they were about 10% of the initial levels; he remained abnormally pigmented, although less so. Case 3 still had high plasma ACTH levels and was slightly pigmented.

TABLE IV—Plasma ACTH concentrations (ng/l) before and after pituitary implantation for Nelson's syndrome

Case No	Before implant			After implant, at last assessment			
	9 am (0 min)	Minutes after usual morning dose of steroids		Midnight	9 am (0 min)	Minutes after usual morning dose of steroids	
		60	120			60	120
1	5449	1082		139	<32		<16
2	322				53		<29
3	365				18		<11
4					616	282	244
5	917	523	119		630		170
7	30 047	13 771	1645		32		320
8		4623	2000		50	54	14
					3139	2498	30
					5154	1250	5889
					736		14 422
					179	<28	<23
							<12
							255

Complications—One patient (case 1) had a 3rd nerve paresis for a few days after the operation, and another patient (case 6) developed a cerebrospinal fluid leak that was successfully plugged by us (table III). He also had diabetes insipidus requiring pitressin until his death. One patient (case 8) with a low basal serum luteinising hormone level of 1.9 U/l (normal range 3 to 8 U/l before implant) developed clinical gonadal deficiency but fathered a child on his current treatment with human chorionic gonadotrophin. One patient (case 5) was thought by another hospital to be hypothyroid and was started on thyroxine. The remaining patients showed normal pituitary function both clinically and as tested by the combined pituitary function test at last assessment.

Histology—In all six patients who underwent biopsy light microscopy showed the presence of a basophil mucoid adenoma generally with moderately to well granulated cytoplasm in cells of small size containing small dense irregular ovoid nuclei. In case 3 nuclei were pleomorphic and vesicular. In case 7 the biopsy specimen in 1972 showed poor cytoplasmic staining while repeat biopsy at the time of reimplantation in 1974 showed moderate to marked granular cytoplasmic periodic-acid Schiff (PAS) positivity. Immunofluorescence

FIG 2—Case 7. Electron micrograph of adenoma. Secretory granules are aligned along the cell membranes of very active cells. G = Granules. ER = Endoplasmic reticulum. N = Nucleus. (□ × 3600.)

staining in cases 2, 7, and 8 was positive to only anti-ACTH, and the pattern of staining corresponded to the distribution of the PAS-positive granules and to the electron-dense granules seen in the electron micrographs (fig 1). Electron microscopy (in cases 2, 5, 7, and 8) showed variable numbers of cytoplasmic granules with typical appearances of ACTH (150-300 nm diameter), sometimes aligned along cell membranes. Endoplasmic reticulum was prominent in cases 2 and 7 but not in cases 5 and 8, which suggested that the latter patients had a lower level of secretory activity (fig 2).

Discussion

The pituitary tumours that accompany Nelson's syndrome are apt to be unusually aggressive and their treatment is far from satisfactory. The number of treated cases reported is small, and it is often difficult to assess the efficacy of any treatment; many cases have been treated with a succession of procedures, which emphasises the resistance of these tumours to treatment. The response to external radiotherapy is on the whole poor, though a minority of patients have a good response.^{1 2 4 11-13} Surgical hypophysectomy has also had variable results.^{2 14} Espinoza *et al*,¹⁵ however, have reported the successful treatment of two out of three patients with Nelson's syndrome by selective removal of the pituitary adenomas. They used a microsurgical technique with a transnasal and transphenoidal approach to the pituitary with television magnification and televised radiofluoroscopic control. Successful treatment of one case of Nelson's syndrome by cryosurgery has been reported.¹⁶ Linfoot and his colleagues^{17 18} treated six patients with Nelson's syndrome with heavy particle therapy. Although three patients had decreased pigmentation, four of the five in whom ACTH was measured still had grossly raised levels. Successful treatment of two cases of Nelson's syndrome with pituitary implant of ⁹⁰Y and ¹⁹⁸Au has been reported.¹⁹

All our patients had decreased pigmentation after their pituitary implant and none developed further pituitary fossa expansion or new cranial nerve involvement. All five patients in whom pre-

FIG 1—Case 7. Immunofluorescent stain for ACTH on paraffin section of adenoma. In some areas (arrowed) the immunostain (white areas) can be seen to outline cells. (□ × 155.)

and post-implant plasma ACTH levels were measured showed reduced levels. Normal levels were reached in four of the six in whom pituitary implantation was the sole treatment. The attainment of normal plasma ACTH levels (below 80 ng/l) seems a desirable objective, but most patients who have had bilateral adrenalectomy for Cushing's disease and who do not have Nelson's syndrome do have raised levels despite adequate replacement therapy.²⁰

The effect of the procedure seems to be long lasting: there were no subsequent relapses, and one patient (case 4) was still in clinical remission with normal plasma ACTH levels 13 years after the pituitary implant. There were few surgical or functional complications of the procedure. Pituitary implant thus compares favourably with the other procedures used for treating Nelson's syndrome.

This series was too small to show which type of radionuclide gave the best results. Each variety of pituitary implant used was followed with at least one good result. We no longer use a combination of ⁹⁰Y and ¹⁹⁸Au as it is technically difficult to insert accurately. Now we initially assess the size of the tumour with plain radiography, lateral hypocyclusoidal tomography, and air encephalography. In cases suitable for a pituitary implant ⁹⁰Y calculated to give a dose of 150 000 rads to the gland periphery is used. If the dorsum sellae is severely eroded there would be inadequate landmarks for implantation; also extension of the subarachnoid space into the pituitary fossa would rule out a pituitary implant because of the danger of a CSF leak, and under these circumstances a transnasal hypophysectomy would be preferred. If the tumour has a large suprasellar extension (>8 mm on air encephalography) the patient would be referred for transfrontal craniotomy. In the event, only two patients were judged more suitable for open surgery.

Two out of four patients showed a clearly normal sella at adrenalectomy, thus showing that it is impossible to exclude the risk of Nelson's syndrome by radiological examination of the fossa. Indeed, one of these patients still had a normal sella at the time of diagnosis of Nelson's syndrome.

From the histopathological viewpoint the present series is the largest so far reported. Nelson *et al*² noted that two of their patients had "chromophobe adenomas," a statement that can be interpreted in the light of our recent findings⁸ as meaning active

poorly granulated ACTH-secreting tumours. Rivière *et al*²¹ reported a case of Nelson's syndrome with light and electron microscopy findings similar to those described here, but no other biopsies seem to have been reported. Muroid ACTH-secreting pituitary adenomas are probably central to this syndrome, but the relation of their origin to any presumptive hypothalamic disturbance is still obscure.

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Comparison of atenolol and propranolol during insulin-induced hypoglycaemia

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Summary

The effects of atenolol, a new beta₁-blocking drug, on pulse rate, sweating, and blood glucose levels during insulin-induced hypoglycaemia were studied in a double-blind crossover trial in eight normal subjects using placebo and propranolol as reference agents. The inten-

sity of induced hypoglycaemia was identical for atenolol, propranolol, and placebo. Propranolol prolonged hypoglycaemia, but atenolol did not. Atenolol may therefore be safe for use in patients receiving insulin.

Introduction

The use of beta-blocking drugs in diabetic patients is contra-indicated because they may intensify hypoglycaemia and prevent the adrenergic signs by which hypoglycaemia is recognised.¹⁻³ The new selective beta₁-blockers, however, specifically antagonise the actions of catecholamines on the heart and may be free of hypoglycaemic side effects. Atenolol (Tenormin) is a recently developed cardioselective beta-blocker with a combination of pharmacological properties not shown by any other beta-

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