Nelson's syndrome; a new look

Leslie R. Sheeler, M.D.
Raymond F. Grenfell, Jr., M.D.
O. Peter Schumacher, M.D., Ph.D.

Department of Endocrinology

Manjula S. Kumar, Ph.D.

Department of Immunopathology

Nelson's syndrome is defined as the development of an ACTH-secreting pituitary tumor following bilateral adrenalectomy for pituitary-dependent Cushing's syndrome.[1, 2] The potential seriousness of these tumors has been repeatedly emphasized.[3–6] Polycycloidal polytomography of the sella allows the detection of minor defects compatible with small adenomas. It is obvious that the patients were not studied this way initially.

We reviewed 38 cases of Cushing's disease, that is, ACTH-dependent adrenocortical hyperplasia treated from 1951 to 1973 at the Cleveland Clinic (*Table 1*). Five men and 12 women who had undergone either total (eight cases) or subtotal (nine cases) adrenalectomy for Cushing's syndrome between 1951 and 1973 were examined from 1976 to 1979. Two additional women treated with yttrium-90 implantation were also studied. The original diagnosis of Cushing's disease was verified in all cases by combining clinical findings with biochemical studies including the standard dexamethasone suppression test (2 mg/day for 2 days followed by 8 mg/day for 2 days, given orally in divided doses). Pathologic findings confirmed the diagnosis in all surgical cases of bilateral adrenal hyperplasia.

Roentgenographic evaluation consisted of polytomography of the sella in all 19 patients. Full

Table 1. Treatment of Cushing's disease; 1951 to 1973; 38 patients

	No. of patients	
Total		38
Treatment directed at pituitary	4	
Adrenal surgery	34	
Deceased	10	
Not contacted	6	
Refused to return	1	
Returned for study	17	

visual field examinations were performed in all 19 patients in the Department of Ophthalmology. Laboratory studies were done at 8:00 a.m., at least 12 hours after the last dose of glucocorticoid therapy.

Assays

ACTH was measured by radioimmunoassay with dextran-coated charcoal to separate bound and free ligand.[7] Reagents for assay were obtained from Amersham Corporation (Arlington Heights, Illinois 60005). Twenty to 30 ml of blood were drawn in plastic syringes containing heparin as an anticoagulant. ACTH was extracted from 8 ml of plasma before assay by absorption on glass particles. The interassay variation at the level of 50 pg/ml was 11.4%, and at the level of 200 pg/ml was 6%. In 25 normal subjects, the mean 8:00 a.m. ACTH level was 18.2 ± 10.2 pg/ml (range, 10 to 52 pg/ml).

Serum luteinizing (LH), follicular stimulating hormone (FSH), and prolactin were measured by double antibody radioimmunoassay procedures. Methods previously described were used with slight modification.[8–10] ^{125}I-labelled LH and FSH, as well as specific antisera to human LH and FSH were purchased from Cambridge Nuclear Corporation (Billerica, Massachusetts 01865). Research Standard 69/104 was obtained from the Medical Research Council, National Institute for Medical Research (Mill Hill, London) and used for both LH and FSH assays. The mean LH and FSH concentrations in 24 premenopausal women at follicular phase were 12.7 ± 5.0 mIU/ml (range, 3.7 to 26), and 10.7 ± 6.0 mIU/ml (range, 2.7 to 27); and at luteinic phase were 12.9 ± 9.0 (range, 2.3 to 38) and 6.4 ± 3.2 mIU/ml (range 1.2 to 15) respectively. In 29 normal men the mean LH level was 11.6 ± 4.0 mIU/ml (range, 5.6 to 28), and FSH level was 8.4 ± 4.2 mIU/ml (range, 3.7 to 20). The interassay variation at the level of 10 mIU and 5 mIU was 7.5% for LH and 7% for FSH, respectively. Reagents for prolactin assay were purchased from Serono Laboratories (Baintree, Massachusetts 02184). The mean prolactin level in 29 normal women was 10.2 ± 4.7 (range, 0.8 to 19.7), and in 21 normal men was 8.3 ± 2.8 ng/ml (range, 2.7 to 13.9). The interassay variation at the level of 7 ng/ml was 6.6 for prolactin assay.

Serum cortisol was measured by a solid phase radioimmunoassay procedure.[10] Reagents for the assay were obtained from Clinical Assays, Inc. (Cambridge, Massachusetts 02139). The interassay variation at the level of 6.0 μg/dl was 6% (c.v.). The mean cortisol level in 52 normal subjects at 8:00 a.m. was 14.4 ± 6.5 μg/dl (range, 8.3 to 29), and at 4:00 to 5:00 p.m. was 9.0 ± 5.4 μg/dl (range, 3.3 to 15).

Results

Table 2 summarizes the results. Hyperpigmentation was evident in 13 of the 17 patients. Of these 13 patients, six had abnormal sella tomograms consistent with a small pituitary tumor and five had normal sella tomograms. Two

Table 2. Patients previously treated for Cushing's disease, LH mIU/ml

Date	Patient	Age	Sex	ACTH pg/ml	Operation (yr)	Serum cortisol μg/dl	Prolactin ng/L	LH mIU/ml	FSH mIU/ml	Remarks
					Hyperpigmented patients with abnormal sella tomograms					
2/77	1	27	F	592	Total (1966)	1.3	60.0	22.0	6.5	Apoplexy, 1977
10/76	2	34	F	750	Subtotal (1965)	14.6	14.0	3.3	3.7	
9/77	3	38	F	250	Total (1966)	1.7	9.0	1.8	2.5	Apoplexy, 1969
11/76	4	36	M	357	Subtotal (1962)	18.0	7.8	31.0	27.0	
10/76	5	49	F	342	Subtotal (1961)	14.5	14.5	113.0	97.0	
4/79	6	38	F	437	Total (1968)	12.3	13.4	15.3	10.2	
					Hyperpigmented patients with normal sella tomograms					
10/76	7	48	M	357	Total (1970)	8.6	12.6	11.5	10.3	
10/76	8	34	F	1428	Subtotal (1962)	1.6	...	2.4	3.2	Apoplexy, 1969
10/76	9	60	M	398	Subtotal (1952)	8.8	8.0	10.0	8.4	
10/76	10	26	F	658	Total (1973)	13.0	9.5	...	...	
4/79	11	52	M	213	Subtotal (1953)	25.4	14.1	5.6	5.7	Recurrent Cushing's disease
					Hyperpigmented patients with previous treatment for pituitary tumor					
9/78	12	51	F	3000	Total (1958) y-90 (1963)	11.5	20.3	...	...	
10/78	13	32	F	604	Total (1973) Transsphenoidal pituary surgery (1976)			...	...	ACTH 2010 before surgery
					Patients with normal pigmentation and normal sella tomograms					
11/76	14	65	M	134	Subtotal (1958)	9.1	6.7	49.0	22.5	
	15	44	F	32	Total (1961)	10.1	13.0	23.2	2.6	
10/76	16	38	F	214	Subtotal (1967)	15.5	...	5.0	5.4	
5/77	17	37	F	49.8	Subtotal (1967)	23.8	7.2	...	...	
					Patients treated with y-90 implantation alone					
12/76	18	51	F	—	Implantation (1963)	<1.25	2.9	<1.25	<1.25	
10/76	19	56	F	18.2	Implantation (1965)	2.6	2.9	2.8	3.8	

patients (12 and 13) had received treatment previously, which made interpretation of the tomograms impossible. Neither of the two patients receiving yttrium-90 implantation as the sole treatment became hyperpigmented (*Table 1*). The four cases of proved tumor included two patients who had clinically occult tumors at autopsy and the two patients who had pituitary treatment for known tumors (patients 12 and 13). The presumed cases were those six with abnormal tomograms plus patient 8 who had a history consistent with pituitary apoplexy.

Twelve of the 13 hyperpigmented patients were taking oral replacement doses of glucocorticoid. Ten patients had taken cortisone acetate and two had taken hydrocortisone. Nine of the 13 patients were taking fluorocortisone acetate. All were believed to be receiving adequate doses without signs or symptoms of adrenal insufficiency. The smallest dose of cortisone acetate was 12.5 mg every 12 hours.

One patient who did not take cortisone (patient 11, *Table 2*) was believed to have clinical Cushing's syndrome 26 years after subtotal adrenalectomy. At physical examination centripetal obesity and thin skin were observed. The results of the 24-hour urine collection showed 1148 g of creatinine, with a 17-hydroxycorticoid value of 12.1 mg/24 hr and an elevated urine-free cortisol value of 380 μg/24 hr. Pituitary irradiation was recommended as treatment for the recurrent Cushing's disease.

Visual fields were normal in 18 of the 19 patients studied. One of the two patients treated with yttrium-90 implantation as initial treatment for Cushing's disease had a left field cut. This cut had been stable and had been present for many years.

Further data on four patients treated with pituitary irradiation following the detection of probable small pituitary tumor are given in *Table 3*.

Discussion

In 1958, Nelson et al[1] described a postadrenalectomy patient in whom progressive enlargement of the sella turcica and intense pigmentation developed. In 1960, Nelson et al[2] reviewed ten postadrenalectomy cases. All ten patients were deeply pigmented and eight had roentgenographic evidence or visual field evidence of a pituitary tumor.

The risk of this pituitary tumor developing after bilateral adrenalectomy for Cushing's disease is reported to be from 0% to 38%.[3, 11, 12] The development of these pituitary tumors, termed Nelson's syndrome, is manifested clinically by progressive sellar enlargement, headaches, visual field defects, elevation of ACTH, cutaneous hyperpigmentation and tendency to pituitary apoplexy. In our series, 13 of 17 patients (76%) had hyperpigmentation after adrenalectomy, and nine of 17 (53%) had both hyperpigmentation and evidence of tumor.

None of our patients had abnormal sella turcica x-ray films before the original adrenal surgery. Whether a small pituitary tumor exists in all patients with Cushing's disease before adrenalectomy is a question that is not yet resolved, but recent evidence suggests the presence of a small pituitary tumor in many cases.[13–15]

Adequate autopsy material was available on four of the ten patients who had died. One of these patients who died one month after the adrenal surgery had a 0.5-cm basophilic adenoma. Another patient who died 12 years after adrenal surgery had a 1.0-cm pituitary eosino-

philic adenoma. The other two patients were believed not to have pituitary tumors. It should be noted that Costello[15] reported a 25% incidence of apparent asymptomatic adenomas in an autopsy series.

Rovit and Berry[4] have pointed out the capacity for aggressive tumor growth from the ophthalmologic standpoint. Twenty-four percent of their patients with Cushing's syndrome and pituitary tumors had extraocular motor palsies, an incidence two to four times greater than is generally experienced with the usual nonsecretory chromophobe adenomas. Other authors believe that another index of this aggressive growth rate is the occurrence of pituitary apoplexy with abrupt cavernous sinus compression.

Three patients with Nelson's syndrome in the present series had historical evidence consistent with spontaneous infarction of a pituitary tumor. Transient ophthalmoplegia developed in two patients at the time of the suspected infarction. Two of these three patients had abnormal sella tomograms. Although pituitary apoplexy is potentially life threatening, none of these three patients required surgery at the time of the event. All three were well at the time of our study.

None of the patients with presumed (7) or proven (4) pituitary tumors following adrenalectomy manifested the clinically malignant course often reported. Since many patients with Cushing's disease appear to have pituitary adenomas at the time of diagnosis,[13, 14] it is not surprising that a follow-up of patients treated 6 to 26 years previously would reveal a high incidence of pituitary adenomas (11 of 23). The fact that all of these 11 patients have done well except for apoplexy in three with transient (1), or permanent (1) diplopia, is striking. Patients 12 and 13 had been treated because they had a known tumor, not because they had serious neurologic sequellae. We have elected to treat four of the patients with conventional cobalt radiation. The posttreatment evaluation is summarized in *Table 3*. The seven patients with presumed pituitary tumors had no indication for neurosurgical intervention. The two patients previously treated for pituitary tumor were doing well at the time of the study. We believe that neurosurgery is not indicated routinely merely because Nelson's syndrome is diagnosed. The published reports on Nelson's syndrome imply otherwise.

Table 3. Results after radiation therapy

Patient	Treatment	Date	ACTH pg/ml	Cortisol g/dl	Prolactin ng/ml	Remarks
1	1250 rads	2/77	592	1.3	60.0	Radiation discontinued by patient after 1250 rads in January of 1978; apoplexy in August 1977
		8/77	35	1.4	4.0	
		9/79	492	1.4	4.2	
2	5000 rads	10/76	750	14.6	14.0	Radiation completed in August 1977
		6/78	396	9.3	...	
3	5000 rads	9/77	250	1.7	9.0	Radiation completed in August 1977
		8/78	57	1.7	...	
4	5000 rads	4/79	437	12.3	15.3	Radiation completed in July 1979
		10/79	497	2.0	12.0	

Summary

Eleven of 21 patients treated with adrenal surgery from 1951 to 1973 for pituitary Cushing's syndrome had presumed (seven) or proved (four) pituitary tumors. Autopsy showed pituitary tumors in two of four patients. Two patients had previously been treated for pituitary tumor. Seventeen additional patients were studied. Six of 11 patients with hyperpigmentation had evidence on sella polytomography of pituitary tumors. The clinical course of these patients has been benign up to this time, leading us to conclude that aggressive neurosurgical treatment does not seem to be routinely indicated.

Acknowledgments

Funds for the study were provided in part by the Reinberger Foundation.

We thank Ms. Anne Morter for her technical assistance.

References

1. Nelson DH, Meakin JW, Dealy JB Jr, et al: ACTH-producing tumor of the pituitary gland. N Engl J Med **259:** 161–164, 1958.
2. Nelson DH, Meakin JW, Thorn GW: ACTH-producing pituitary tumors following adrenalectomy for Cushing's syndrome. Ann Intern Med **52:** 560–569, 1960.
3. Cohen KL, Noth RH, Pechinsk T: Incidence of pituitary tumors following adrenalectomy. Arch Intern Med **138:** 575–579, 1978.
4. Rovit RL, Berry R: Cushing's syndrome and the hypophysis: a reevaluation of pituitary tumors and hyperadrenalism. J Neurosurg **23:** 270–295, 1965.
5. Jordan RM, Cook DM, Kendall JW, et al: Nelson's syndrome and spontaneous pituitary tumor infarction. Arch Intern Med **139:** 340–342, 1979.
6. Salassa RM, Kearns TP, Kernohan JW, et al: Pituitary tumors in patients with Cushing's syndrome. J Clin Endocrinol Metab **19:** 1523–1539, 1959.
7. Herbert V, Lau KS, Gottlieb CW, et al: Coated charcoal immunoassay of insulin. J Clin Endocrinol **25:** 1375–1384, 1965.
8. Kumar MS, Deodhar SD: Radioimmunoassay for pituitary gonadotropins: Luteinizing hormone and follicle stimulating hormone. Manual of Clin Immunol. Rose NR, Friedman H (eds). Publication of Am Soc Microbiol 1976, pp 206–212.
9. Sinha YN, Selby FW, Lewis UJ, et al: A homologous radioimmunoassay for human prolactin. J Clin Endocrinol Metab **36:** 509–516, 1973.
10. Tilden RL: New advantageous approach to the direct radioimmunoassay of cortisol. Clin Chem **23:** 211–215, 1977.
11. Orth DN, Liddle GW: Results of treatment in 108 patients with Cushing's syndrome. N Engl J Med **285:** 243–247, 1971.
12. Moore TJ, Dluhy RG, Williams GH, et al: Nelson's syndrome: frequency, prognosis, and effect of prior pituitary irradiation. Ann Intern Med **85:** 731–734, 1976.
13. Tyrrell JB, Brooks RM, Fitzgerald PA, et al: Cushing's disease; selective trans-sphenoidal resection of pituitary microadenomas. N Engl J Med **298:** 753–758, 1978.
14. Salassa RM, Laws ER Jr, Carpenter PC, et al: Transsphenoidal removal of pituitary microadenoma in Cushing's disease. Mayo Clin Proc **53:** 24–28, 1978.
15. Costello RT: Subclinical adenoma of the pituitary gland. Am J Pathol **12:** 205–216, 1936.