Therapeutic problems with transsphenoidal pituitary surgery for Cushing's disease

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Safe, definitive treatment of Cushing's disease is now possible via total hypophysectomy or selective removal of an adenoma with transsphenoidal surgery.[1-5] The short-term efficacy of pituitary tumor resection has been well demonstrated, although long-term data are lacking. Tyrrell et al[2] suggested that some of these tumors may be too small to detect by current neuroradiologic techniques. Reported complications have included hemorrhage at the operative site,[2, 3] and prolonged postoperative need for glucocorticoid replacement (slow hypothalamic-pituitary-adrenal axis recovery).[1-4]

In our study, 18 patients underwent either selective adenoma removal or total hypophysectomy for Cushing's disease. Our purpose was to evaluate postoperative results of transsphenoidal surgical therapy as well as to record the radiologic data and complications associated with the procedure. We confirmed that initial cure is possible in a large percentage of the patients undergoing this form of therapy. In our series, however, as in all previous studies, not all patients were cured. Our data demonstrated that the tumors responsible are often too small to detect, even with current neuroradiologic techniques. Thus, patients were often selected for surgical therapy on the basis of biochemical criteria. In the present series, operative mortality was zero.

However, we have encountered some morbidity not emphasized in prior reports. A crucial and disturbing finding was the recurrence of active Cushing's disease in 2 patients after initial cure.

Patient population: preoperative and postoperative studies

Eighteen patients (14 women, 4 men; age range, 17–65 years) with the diagnosis of pituitary Cushing's disease underwent transsphenoidal pituitary exploration between 1976 and 1981. The diagnosis of hypercortisolism was based upon clinical presentation of the patient, elevated basal 24-hour urinary 17-hydroxycorticoids, and free cortisol as well as elevated serum cortisol levels.

Sella turcica polytomograms were obtained in 14 patients and interpreted as abnormal in 6. Sector CT scans in 6 patients showed no abnormalities. Each patient was studied for clinical and biochemical response postoperatively. *Table 1* lists the preoperative and postoperative A.M. and P.M. serum cortisol levels and 24-hour urinary 17-hydroxycorticoid and free cortisol measurements. Also shown are preoperative serum ACTH and 24-hour urine collections for 17-hydroxycorticoid and free cortisol levels after high-dose dexamethasone suppression (2 mg, orally, every six hours, for two days). Patients underwent postoperative biochemical evaluation (*Tables 2 and 3*) with either no glucocor-

Table 1. Adrenal function preoperatively

	Serum cortisol μg/dl		Urinary 17-hydroxycorticoids		Urinary free cortisol		
	A.M.	P.M.					
	normal range:						
Patient	(8.2–29) —	(3.3–15)	Baseline (normal: 2–6 mg/24 hr)	End of high dose dex mg/24 hr	Baseline (16–100 μg/24 hr)	End of high dose dex μg/24 hr	Serum ACTH (normal: 6–52 pg/ml)
1	30		10	N.D.	110		40
2	33		8	3.2	67		110
3	23		13.4	2.9	171	22	74
4	29	21.1	11.6	9.2	116		102.8
5	31		44.1	12.0	1445		119
6	22		23.8	2.0	ND		77
7	44.2	26.7	28.6	22.0	256	313	98
8	31		10.4	7.6	170	4	65
9	29.5	34.2	16.2	9.8	135		149
10	50		14.8	2.1	244	16	ND
11	32		24.7	3.8	144	18	
12	40.3		14.3	2.9	92	31	30.2
13	44		22.5	8.6	621	10	119
14	17	17.8	11.7	0	724	83	20
15	34		18.3	1.5	83	5	23
16	10.2	12.2	23.0	5.6	146.5	14	130.5 105.7
17	22.4	28.1 42.6	34.8	15.7	1,033	272.6	72 80
18		11.6	16.5	1.1	275	15.5	88

Dex = dexamethasone; ACTC = adrenocorticotropic hormone; ND = none detected.

Table 2. Adrenal function postoperatively

Case and date of surgery	Serum cortisol, μg/dl A.M normal range: (8.2–29)	Serum cortisol, μg/dl P.M normal range: (3.3–15)	Urinary 17-hydroxy-corticoids (normal: 2–6 mg/24 hr)	Urinary free cortisol (normal range: 16–100 μg/24 hr)
1 (8/7/79)	15.8 (5/80)		5.2 (2/80) 3.9 (5/80)	19.9 (2/80)
2 (8/30/78)			0.2 (10/81)	<1.8 (10/81)
3 (8/18/78)*		17.2 (10/81) 17.8 (4/82)	4.0 (11/79) 10.0 (11/81) 15.3 (1/82)	54 (5/79) 182 (11/81) 449 (1/82)
4 (3/1/79)		<2.5 (9/81)	<5	
5 (5/10/79)		11.9 (9/81) 7.1 (10/80)	3.3 (9/81)	
6 (3/31/80)	<2.5 (8/80)	3.3 (8/80)		
7 (12/3/79)	6.0		0.6 (2/80)	12.3 (2/80)
8 (7/8/80)	<2.5 (9/80)			
9 (12/10/79)	<2.5 (7/80)	<2.5 (7/80)	None detected (7/80)	10.6 (7/80)
10 (3/29/76)	3.7 (11/78)		1.2 (11/78)	3.2
11 (2/77)*		21.8† (2/81)	15.6 (7/81)†	165 (7/81)†
12 (7/79)	7.1 (8/79) 9.6 (3/80)	16 (3/80)		
13 (4/19/79)†	42.0 (5/79)†		55.7 (5/79)†	1900 (5/79)†
14 (6/27/79)†	24.5† (9/79)		15.2 (9/79)†	56 (11/79)
15 (3/13/80)†	21.4† (11/80)	27.9 (1/81)	9.9 (1/81)†	170 (1/81)†
16 (10/6/81)	3.1 (10/81)	3.9 (11/81) <2.5 (10/81)	4.9 (11/81)	49 (11/81)
17 (8/27/81)	<2.5 (8/81)	<2.5 (8/81)	1.9 (9/81)	11 (9/81)
18 (7/10/81)	3.2 (10/81) <2.5 (11/81) 4.0 (12/81) 7.2 (1/82)		None detected (10/81) 1.7 (9/81) 2.6 (11/81)	25.7 (10/81) 65 (11/81) <6.7 (10/81)

* Not cured, recurrence.

† Not cured, persistence.

Table 3. Pituitary function; postoperative

Pt no. (date of surgery) sex	ACTH (normal: 6–52 pg/ml)	T-4 (normal: 5–12 μg/dl)	TSH (normal: <2–6 μU/ml)	FSH (mIU/ml) (fp: 2.7–27.0 lp: 1.2–15.0)*	LH (mIU/ml) (fp: 3.7–26.0 lp: 1.2–15.0)*	Testosterone (normal male: 370–1100 ng/dl)	Prolactin (normal: <22 ng/ml)
1 (8/7/79) F	23.6 (11/12/79)			50.3 (9/19/79)	22.0 (9/19/79)		
2 (8/30/78) F		6.1 (10/12/78)	4.7 (10/12/78)	51.0 (5/3/79)			
3* (8/18/78) F		5.6 (10/78)		13.3 (8/82)			
		7.0 (7/80)		Normal menses			
4 (3/1/79) F		4.4 (3/5/79)					
		3.7 (4/5/79)	<2.0 (4/5/79)	4.1 (9/8/81)	<4.0 (9/8/81)		
5 (5/10/79) F		8.2 (9/25/81)		Menses normal, had baby			
6 (3/31/80) M		6.3 (10/16/80)				344 (4/81)	
						747 (7/82)	
7 (12/3/79) F		9.4 (2/80)	3.0 (12/14/79)	64.2 (2/80)			
8 (7/8/80) F	29.0 (7/12/80)	9.6 (7/12/80)		4.6 (7/29/80)			
	23.8 (9/3/80)	7.2 (7/29/80)		22.0 (7/12/80)			
		4.2 (9/3/80)					
		17.4 (1/13/81)†					
9 (12/10/79) M	19 to 31 to 48						
	(On metapyrone)	5.4 (3/80)	3.3 (7/11/80)	6.6 (3/80)	23.5 (7/80)	860 (7/80)	8.5 (12/18/79)
				11.4 (7/80)			
10* (3/29/76) F	<13	1.6 (6/76)					3.8 (11/20/78)
11 (2/3/77) M	63(2/22/79)	1.7 (2/28/79)	<2.0 (2/22/79)	5.9 (2/22/79)	3.8 (2/22/79)	93 (3/9/79)	
			On replacement			80 (2/20/78)	
12 (7/26/79) F	30.2 (8/1/79)	3.0 (9/21/79)		3.1 (12/5/79)			
		3.4 (12/5/79)					
		16.6 (3/80)†					
13‡ (4/19/79) F	306.4 (8/31/81)	9.0 (10/30/79)†	<2.0	No menses			
14‡ (6/27/79) F		9.6 (8/79)†	2.0	13 (9/79)			
		3.4 (7/79)		Hysterectomy, BSO, 1975			
15‡ (3/13/80) F		4.7 (3/20/80)					
		2.0 (3/27/80)					
		12.4 (4/28/80)‡					

16	(10/6/81)	F		8.0 (11/10/81)		Normal menses		
17	(8/27/81)	F	<37.5 (9/11/81)	7.6 (10/5/81)		Normal menses		
18	(7/10/81)	F	42.7 (9/29/81)	6.4 (12/7/81)		19.4 (3/31/82)	6.3 (10/13/81)	8.4 (10/13/81)
			<37.5 (11/6/81)					

* Not cured, recurrence.
† On thyroid replacement.
‡ Not cured, persistence.
Fp = follicular phase; lp = luteinic phase; BSO = bilateral salpingo-oophorectomy.

ticoid coverage or while on dexamethasone. *Clinical cure was defined as reversal or marked reduction of hypercortisolism.* This included weight loss, redistribution of body fat, resolution or marked improvement in proximal muscle myopathy, fading of dermatologic manifestations, and either correction or improvement of hypertension and glucose tolerance.

Methods

Urinary 17-hydroxycorticoids were measured by standard techniques.[6] Serum cortisol levels were obtained by a simplified radioimmunoassay method reported by Tilden.[7] Thyroxine measurements (T_4) were performed by radioimmunoassay in unextracted serum as described by Chopra,[8] and ACTH measurements were performed as described by Berson and Yalow.[9] Serum testosterone results were performed by radioimmunoassay without chromatography as described by Ismail et al,[10] and the radioimmunoassay for prolactin was done via Sinha et al.[11] Radioimmunoassays for luteinizing hormone (LH) and follicle stimulating hormone (FSH) were performed by the method of Kumar and Deodhar.[12] For determination of urinary free cortisol, 100 ml of sample was extracted with 2 ml of dichloromethane (CH_2Cl_2) and 50 ml of extract was directly dried in antibody-coated tubes that were run in solid-phase cortisol radioimmunoassay. Dexamethasone suppression tests were performed after baseline urine and serum measurements were made in all patients preoperatively. This included the dexamethasone low-dose suppression test (0.5 mg dexamethasone every six hours, orally, for 48 hours) followed by the high-dose dexamethasone suppression test (2.0 mg dexamethasone every six hours, orally, for 48 hours). Twenty-four hour urine collections and measurements were

made on the second day of the low-dose and high-dose suppression tests; results of the high-dose suppression studies are reported in *Table 1*.

Results

Eighteen patients ranging in age from 17 to 65 years with Cushing's disease underwent transsphenoidal microsurgical pituitary exploration from 1976 to 1981 at the Cleveland Clinic. Follow-up ranged from 3 to 48 months; mean, 22 months. Eleven patients had histologic confirmation of a pituitary tumor. Of the 8 patients with normal sella tomograms, 5 (62%) had pituitary tumors at surgery confirmed histologically. Of the 6 patients with abnormal sella tomograms preoperatively, 3 (50%) had pituitary tumors at surgery confirmed histologically. Immediately postoperatively, 15 patients had clinical and biochemical evidence of cure but 3 patients did not. Patient 2 showed initial cure but exhibited clinical and biochemical evidence of recurrence approximately 20 months postoperatively. He is presently being managed medically. Patient 3 was also cured initially, but had clinical and biochemical proof of recurrence 37 months later (*Table 2*) and then underwent bilateral adrenalectomy. Thus, 13 of 18 patients (72%) were considered clinically cured. Of those not cured, patient 15 underwent a second transsphenoidal operation with a total hypophysectomy, and patients 13 and 14 had bilateral adrenalectomy.

All patients preoperatively had biochemical evidence of Cushing's disease (*Table 1*) and 13 of 18 patients (72%) had laboratory evidence of cure (*Table 2*). Eight patients (cases 4, 8, 10–15) (*Table 3*) had permanent hypopituitarism. All cured patients required cortisone replacement therapy postoperatively. Glucocorticoid therapy was withdrawn after four to eight months except in patients with permanent hypopituitarism. Of the 13 cured patients, 9 have normal pituitary function with no need for thyroid or cortisone replacement.

Major complications were cerebrospinal fluid leaks in 4 patients (22%), anosmia in one (6%), perforated nasal septum in one (6%), and meningitis in 2 (11%). Diabetes insipidus developed postoperatively in 8 patients (44%) but was eventually resolved in all of them.

Discussion

Since 1932 when Cushing[13] reported pituitary adenomas at autopsy in 6 of 8 patients with hypercortisolism, the treatment of this disease has been controversial. The advent of microsurgery made it possible to direct curative therapy to the pituitary gland. It appears from our series and from most of the literature that the decision to explore the pituitary should be based on biochemical data.[2-5] There is a high incidence of false-negative neuroradiologic studies in patients who have ultimately been proved to have small pituitary adenomas causing the Cushing's disease.[2-5] Also, one suspects a strong possibility of false-positive neuroradiologic studies since up to 27% of pituitary glands at autopsy contain adenomas.[14] Salassa et al[1] reported at least one false-positive neuroradiologic study. In their series of 22 patients with clinical hypercortisolism small pituitary tumors were visualized in 18 patients via triaxial spiral tomograms and bilateral carotid angiograms with magnification and subtraction techniques.

In 16 of these 18 patients undergoing transsphenoidal surgery, there were no immediate recurrences. However, only the patients with radiographic abnormalities had been selected for surgery.

Carmalt et al[4] described 13 patients

treated for Cushing's disease with transsphenoidal hypophysectomy. All had had normal sellas radiographically. On review of the 12 survivors 2–11 years later, 11 were in complete remission. Tyrrell et al[2] had similar results with transsphenoidal microsurgical pituitary exploration in 20 consecutive patients with Cushing's disease, 8 with normal sella tomograms. Hypercortisolism was corrected in 17 patients (85%). They concluded that the majority of patients with Cushing's disease have ACTH-secreting pituitary microadenomas and that the hypothalamic abnormalities of ACTH regulation are a consequence of hypercortisolism rather than a primary central nervous system abnormality. Selective removal of the adenoma rapidly corrects the hypercortisolism in most patients.[2] An updated report[5] cites an additional 52 cases. Of the 59 patients with pituitary microadenomas undergoing pituitary microsurgery, 48 (81%) were cured by selective removal of the adenoma and 7 (12%) by total hypophysectomy; disease persisted in 3 patients (5%); one (2%) had recurrence. Of 13 cases of extrasellar extension of the tumor, 3 (23%) were corrected by selective removal of the tumor, one (8%) was corrected with total hypophysectomy, disease persisted in 6 (46%), and there were 3 recurrences (23%).

Bigos et al[3] described 24 transsphenoidal pituitary explorations for Cushing's disease. Ten patients had normal sellas by radiographic assessment; 16 (67%) were considered cured over a median follow-up period of 12 months (range, one month to 15 years). They also pointed out that the likelihood of curing Cushing's disease by transsphenoidal surgery is closely related to tumor size. None of their 3 patients with partial or complete invasion of an enlarged sella turcica was cured. Two patients with initial remission had recurrences 10 and 20 months after surgery, respectively. They concluded that extended observation over many years is required to determine success.

Our 18 patients were selected for pituitary surgery on the basis of biochemical criteria. Initially, 15 were considered cured by clinical and biochemical criteria. Two patients (3 and 11) had recurrence 20 and 37 months after transsphenoidal surgery (*Table 2*). Our surgical results are closest to those of Bigos et al[3] (72% and 67%, respectively). Our patients did experience some morbidity; 4 patients had cerebrospinal fluid leaks necessitating repair. One patient with cerebrospinal fluid leak and meningitis had received 4500 rads external radiation 18 months prior to surgery. In a recent unpublished review (personal communication) of the 103 transsphenoidal pituitary operations performed for various reasons at the Cleveland Clinic from 1975 to 1980, there were 10 patients with cerebrospinal fluid leaks (10%); 4 with Cushing's disease; 3 with metastatic carcinoma; one with acromegaly; and 2 patients with "nonfunctioning" chromophobe pituitary adenoma, one of whom had undergone radiotherapy prior to surgery.

All cured patients required postoperative glucocorticoid replacement initially. Four of these patients will need life-long cortisone, thyroid hormone, and sex steroid replacement. Other complications included meningitis in 2 patients (11%), anosmia in one (6%), and perforated nasal septum in one patient (6%). Diabetes insipidus occurred postoperatively in 8 patients (44%), but was resolved in all. Of the 5 patients not cured by transsphenoidal pituitary surgery as the initial form of therapy (persistence or recurrence of disease) 3 (cases 3, 13, and 14) underwent bilateral ad-

renalectomy. All had histologic evidence of adrenal hyperplasia. Two of these patients (cases 13 and 14) had evidence of hypopituitarism with a low T_4, amenorrhea, and low gonadotrophins prior to adrenalectomy. We suspect, but have been unable to prove, that these patients had ectopic ACTH syndrome. As mentioned above, patient 11 was initially cured, but showed evidence of recurrence of disease and has been managed medically. The fifth patient with recurrence (case 15) underwent a second transsphenoidal hypophysectomy. No adenoma had been found at the initial procedure, but at the second, an ACTH-staining pituitary tumor was removed.

The high incidence of hypopituitarism results from the decision to be more aggressive in seeking a permanent cure of older patients. The one exception was patient 4 who was only 20 years of age at the time of surgery. A total hypophysectomy was necessary in her case because the pituitary had been entirely replaced by tumor.

Our radiologic data showed that 14 patients had undergone sella polytomography; tomograms in 8 patients (57%) were reported as normal and in 6 (43%) as abnormal. Of the 8 patients with normal polytomograms, 5 (62%) had pituitary adenomas at surgery and of the 6 patients with abnormal studies, 3 (50%) had pituitary adenomas at surgery. Six patients had normal sector CT scans, but at surgery, tumors were found in 5 (83%).

In summary, we believe that transsphenoidal pituitary surgery is an effective, but less than perfect therapy for most, if not all, patients with pituitary ACTH hypersecretion, or Cushing's disease. Sella tomography was of little or no diagnostic benefit and sector CT scanning in 6 patients was also nondiagnostic. There was no mortality associated with transsphenoidal surgery in our patients, but some morbidity was observed.

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