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The Longitudinal Course of Psychopathology in Cushing's Syndrome after Correction of Hypercortisolism

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ABSTRACT

Endogenous Cushing's syndrome (CS) is associated with significant psychopathology during the course of the disease. The purpose of this study was to evaluate the psychological and endocrine status of patients with CS after correction of their hypercortisolism. Thirty-three patients with active CS were examined before and at 3 months (28 patients), 6 months (25 patients), and 12 months (29 patients) after correction of hypercortisolism. Before cure, 66.7% of the patients had significant psychopathology, with the predominant diagnosis of atypical depressive disorder (AD) in 51.5% and/or major affective disorder in 12%. After cure, overall psychopathology decreased significantly to 53.6% at 3 months, 36% at 6 months, and 24.1% at 12 months, when there was a parallel recovery of the hypothalamic-pituitary-adrenal axis assessed by serial morning ACTH stimulation tests. There was an inverse correlation between psychological recovery and baseline morning cortisol, but no correlation with ACTH-stimulated cortisol values at 60 min. AD continued to be the prevailing diagnosis after correction of hypercortisolism, whereas the frequency of suicidal ideation and panic increased. The presence of AD before and after correction of hypercortisolism might be due to glucocorticoid-induced suppression of hypothalamic CRH secretion. The slight increase in the incidence of panic after correction of hypercortisolism might be due to a decreased glucocorticoid restraint at the central arousal/sympathetic catecholaminergic system. We conclude that CS is associated with AD symptomatology, which gradually improves with time after correction of hypercortisolism. Health care providers should be aware of changes in symptomatology, including suicidal ideation and panic attacks, that occur in a subgroup of patients. (*J Clin Endocrinol Metab* **82:** 912–919, 1997)

CUSHING'S syndrome (CS) includes depressive symptomatology as a part of its clinical spectrum (1–5). These patients have the atypical subtype of depression (6), which apparently is distinct from melancholia (7, 8). Depressed patients with melancholic symptoms exhibit hypophagia and hyposomnia, which have been associated with increased CRH secretion; alternatively, depressed patients with atypical depression present with irritability, hyperphagia, hypersomnia, and increased fatigue, which have been associated with decreased CRH secretion (9). To date, the coexistence of atypical depression and low hypothalamic CRH secretion has been shown or inferred in patients with active CS (10), seasonal affective disorder (11), the chronic fatigue/fibromyalgia syndromes (12, 13), and the postpartum blues/depression syndromes (14). Although the common belief is that depression remits with the "cure" of CS and the correction of hypercortisolism, few studies have prospectively examined the psychological profiles of patients with CS after correction of the hypercortisolemic state. In general, these studies reported that symptoms of depression decreased after cure in some, but not all, patients (2–4, 15, 16).

In an earlier report we showed that over 50% of patients with active CS present with symptoms of atypical depression (6), a phenomenon compatible with the fact that patients with active CS exhibit glucocorticoid-induced suppression of their CRH neurons (9, 10, 17). Thus, the possibility exists in these patients that atypical depression is a result of high concentrations of cortisol, low concentrations of CRH, or both. In the majority of patients with CS, the function of the CRH neuron gradually returns to normal within 12 months after curative surgery, while the patients are receiving daily glucocorticoid replacement (17). The time course of alleviation of the symptoms of atypical depression as well as other less frequent psychopathology symptoms after the correction of chronic hypercortisolism remains unknown or, at best, unclear.

The purpose of this investigation was 3-fold: first, to determine the longitudinal psychological course of patients with CS 3, 6, and 12 months after correction of hypercortisolism; second, to determine whether the recovery of the hypothalamic-pituitary-adrenal (HPA) axis, as indicated by morning cortisol levels and/or cortisol response in an ACTH stimulation test, was related to psychological recovery; and third, to define whether psychopathology before or during

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CS or the duration of CS was related to the occurrence or intensity of psychopathology after cure.

Subjects and Methods

Subjects

The patient group (n = 33) included 28 women and 5 men consecutively admitted to the NIH Clinical Center for the evaluation and treatment of CS. The sample has been described previously (6). In brief, subjects ranged in age from 19–50 yr (mean, 36.4; SD, 9.1). Thirty-one patients were Caucasian, and 2 were African-American. Twenty-nine of the patients had Cushing's disease (pituitary adenoma), 3 had the ectopic ACTH syndrome, and 1 had an adrenal adenoma. On the average, patients had symptoms of CS for 5.63 yr (SD = 4.7), as determined from the medical history. One third (n = 11) of the patients had had at least 1 previous surgery for an unsuccessful pituitary adenoma resection, and 1 of the 11 also had irradiation to the pituitary. After admission to this institution, 22 patients had pituitary adenoma resection, 4 had bilateral adrenalectomy, 2 had pituitary irradiation, and 2 had thoracotomy for resection of an ectopic ACTH-secreting tumor. After remission of hypercortisolism at 3, 6, and 12 month follow-up, as many as 6 patients routinely saw a therapist, 7 reported taking antidepressants or antianxiolytics, and 2 reported psychiatric hospitalizations.

Protocol

The study was approved by the institutional review board. Written informed consent was obtained from each subject. Eligibility criteria included fluency in English; age between 18–50 yr; documented CS by elevated morning and evening serum cortisol levels, elevated 24-h 17-hydroxycorticosteroids per g creatinine excretion, and elevated 24-h urinary free cortisol (UFC) excretion per m^2 body surface area (micrograms per m^2); findings from bilateral inferior petrosal sinus sampling; computed tomography and magnetic resonance imaging scans as appropriate; and surgical and pathological findings.

Design

A prospective longitudinal study was conducted. Patients participated in the psychological testing during the 2-week diagnostic phase of their hospital admission (time 1). All patients had documented CS and were hypercortisolemic at the time of the first interview. Follow-up psychological testing was completed during repeat hospital admissions 3, 6, and 12 months after treatment. Twenty-eight patients were surgically cured by our previously established criteria, with a morning plasma cortisol level less than 3 μg/dL and a UFC less than 20 μg/day on day 4 or 5 postoperatively. These patients were placed on glucocorticoid replacement (12–15 mg hydrocortisone/m^2 body surface area·day) until their 60-min cortisol response to ACTH-(1–24) became 18 μg/dL or more, or indefinitely in the patients treated with bilateral adrenalectomy. The level of 18 μg/dL represents 2 SD below the mean cortisol response in healthy subjects (18). Five patients treated with pituitary irradiation and/or medically with an adrenolytic agent or a steroidogenesis enzyme inhibitor were considered cured if their UFC was within the normal range (20–90 μg/day or $<$70 μg/m^2 body surface area·day).

Psychological and endocrine evaluation

All measures employed have been used extensively in psychiatric research and in clinical settings and have good reliability and validity. The interviews described in the following paragraphs were conducted by the first author, who was trained in the administration of the instruments.

Interviews

Schedule of Affective Disorders and Schizophrenia–Lifetime Version (SADS-LA). The SADS-LA (19) is an interview focusing on psychiatric diagnoses that are based on both the Diagnostic and Statistical Manual IIIR (20) as well as research diagnostic criteria (21). In determining psychiatric diagnoses, the criterion of organic factors as a cause of psychopathology was eliminated. That is, patients could still receive a diagnosis of depression even though there was a presumed endocrine cause. Thus, we could examine the full range of psychopathology exhibited, regardless of its presumed endocrine cause. Interrater agreement on the presence or absence of a psychiatric diagnosis was made on approximately 32% of the posttreatment interviews throughout the course of the study. The average κ coefficient (22) was 0.87.

Atypical Depression Diagnostic Scale (ADDS). The ADDS (23) is an interview designed to ascertain symptoms of depression that reflect reverse vegetative features such as hyperphagia and hypersomnia rather than the hypophagia and hyposomnia often expressed in major depressive disorder of the melancholic type. Mood reactivity is one of the key features assessed by the interview along with rejection sensitivity. The ADDS categorizes subjects as follows: 4 = definite atypical depression; mood reactivity was 50% or more, and two or more symptoms were positive (*e.g.* hyperphagia, hypersomnia, severe fatigue, leaden paralysis, *etc.*); 3 = probable atypical depression; mood reactivity was 50% or more, and one symptom was positive; 2 = simple mood reactive depression; mood reactivity was 50% or more, but no symptom was positive; 1 = no atypical depression; mood reactivity was less than 50%. If a subject was not depressed, a score of 0 was assigned. In this report, a diagnosis of atypical depression was given if the patient scored 3 or 4 on the interview.

The Hamilton Rating Scale for Depression. The Hamilton Rating Scale for Depression (24) consists of 21 items and yields scores of depression severity from 0–65. Scores greater than 20 generally coincide with major depression, whereas those between 12–20 may indicate depressed mood or subsyndromal depression.

Self-report instruments

Symptom Checklist 90-revised (SCL-90R) (25) requests that subjects rate the amount of discomfort experienced over the last week that resulted from the stated 90 items (*e.g.* headaches, crying easily, feeling annoyed or irritated). The scale yields 9 primary symptom dimensions as well as 3 global indexes of distress. Scoring of the instrument was based on nonpsychiatric patient norms. *t* scores are reported. Thus, the mean is indicated by a score of 50, and the SD is 10. The psychotic subscale does not indicate a diagnosis of psychosis, but, rather, refers to symptoms of withdrawal and social isolation. Higher scores indicate higher distress or disturbance on the dimension described.

Profile of Mood States (POMS). POMS (26) requests that subjects rate how they have been feeling over the past week on 65 adjectives (*e.g.* grouchy, anxious, guilty). Six independent factors can be scored from the instrument as well as a total mood disturbance score. Higher scores indicate higher distress or disturbance on the dimension described.

State Trait Anxiety Inventory. The State Trait Anxiety Inventory (27) uses a 4-point Likert scale for 20 items measuring state anxiety and 20 items measuring trait anxiety. Computed scores were based on norms of nonpatient adults. A higher score indicates higher anxiety.

Endocrine assessment and medical information

Recovery of the HPA axis was determined from the baseline morning serum cortisol level and the cortisol response to an ACTH stimulation test. All patients were changed from their usual replacement dose of hydrocortisone (12–15 mg hydrocortisone/m^2 body surface area·day) to an equivalent dose of dexamethasone approximately 1 day before the ACTH test. An iv catheter was inserted between 0700–0800 h, 1 h before the administration of 250 μg cosyntropin (Cortrosyn, Organon, West Orange, NJ). Serum was drawn at baseline (0 min) and 30 and 60 min post-ACTH administration. Serum cortisol (28) was measured by RIA as previously described. The detection limit of the assay ranged from 5–28 nmol/L. Intra- and interassay coefficients of variation were 5% and 11%, respectively. Recovery of the HPA axis was defined as reaching a cortisol concentration of 18 μg/dL or more 30 min or 60 min after ACTH administration (16).

The duration of CS was determined from the medical history of the patient.

Statistical analysis

SPSS-X (29) was used in all statistical analyses. Measures of central tendency and frequency distributions were used to describe the sample. Spearman's ρ or Pearson's correlation coefficients were used to examine relations among the response of the HPA axis, previous psychiatric diagnoses, and current psychopathology. Repeated measures ANOVA or covariance was used to examine trends across time (linear, quadratic, and cubic) for the continuous measures of psychopathology. Cohran's Q was the nonparametric test to determine repeated measures of the presence or absence of a psychiatric diagnosis. McNemar's tests were used for pairwise comparisons to determine where the differences were found across time. The level of significance was set at $P \leq 0.05$.

Results

Patient attrition varied across the study. Many of the patients lived out of state and thus were unable to return for each follow-up, whereas others did not return because they felt they were cured. At the 3 month posttreatment visit, 28 (84.9%) of the 33 patients returned; at 6 months posttreatment, 25 (75.8%) returned; and at 12 months posttreatment, 29 (87.9%) subjects returned. Subjects who did not complete the longitudinal study were not significantly different ($P > 0.05$) from those who did complete the study on the initial measures of state and trait anxiety and anger, the Hamilton Rating Scale for Depression, intelligence quotient, socioeconomic status, or presence or absence of any other psychiatric diagnosis.

Longitudinal psychological course of patients with CS

Psychiatric diagnoses. Table 1 shows the medical diagnosis, psychiatric diagnoses, and response to the ACTH stimulation test for each patient across the study period. [Cross-sectional data from time 1 (active CS) were reported in detail previously (6) and are summarized here.] At the initial hospital admission at this institution, 18 of 33 (54.6%) patients met criteria for a psychiatric illness using Diagnostic and Statistical Manual IIIR or research diagnostic criteria. Of these 18 patients, 17 were categorized as having atypical depression; 3 of them also met criteria for major depression, and 5 of them met criteria for other psychiatric disorders (*e.g.* hypomania, panic, and drug and alcohol abuse). Comorbidity was evident; thus, reported diagnoses do not represent individual patients.

At the 3-month visit, 15 (53.6%) met diagnostic criteria for a psychiatric illness. Of the 28 returning, 7 (25%) met criteria for atypical depression, 9 (32.1%) met criteria for MDD, 2 (7.1%) met criteria for an anxiety disorder, and 3 (10.7%) reported suicidality.

At the 6 month posttreatment visit, 9 (36%) met criteria for a psychiatric illness. Diagnoses in the 25 returning patients included 8 (32%) with atypical depression, 3 (12%) with MDD, 2 (8%) with drug or alcohol abuse, and 1 (4%) with suicidality.

At the 12 month posttreatment visit, 7 subjects (24.1%) met diagnostic criteria for a psychiatric illness. Diagnoses in the 29 returning patients included 5 (17.2%) with atypical depression, 2 (6.9%) with MDD, 1 (3.5%) with drug abuse, and 1 (3.5%) who reported suicidality.

In the longitudinal sample, Cochran's Q was used to determine whether there was an increase or decrease across time for the presence of a psychiatric diagnosis. For atypical depression, there was a significant decrease across time in the number of individuals reporting this disorder [$Q = 10.8$; df(3,22); $P = 0.013$]. Pairwise comparisons using McNemar's test shows that the presence of atypical depression was significantly higher at time 1 (active CS) *vs.* 3 months posttreatment ($P = 0.039$) and higher at time 1 *vs.* 12 months posttreatment ($P = 0.013$). There also was a trend, although not significant, for a decrease across time in the presence of any diagnosis using the SADS-LA [$Q = 7.2$; df(3,24); $P = 0.066$]. Pairwise comparisons using McNemar's test showed that the presence of a psychiatric diagnosis was significantly different when comparing 3 months posttreatment *vs.* 12 months posttreatment ($P = 0.039$).

Across the study, 4 patients had no history of a psychiatric disorder before or during CS, yet did exhibit a disorder following correction of hypercortisolism. Four patients never had a psychiatric diagnosis, and 11 patients had a diagnosis throughout the course of their illness and also after correction of hypercortisolism.

For the Hamilton ratings, there were no significant differences in depression severity across time ($F = 1.2$; $P = 0.36$) using a repeated measures ANOVA.

Self-report instruments. Repeated measures ANOVA with polynomial trends was computed on the longitudinal sample to determine changes in self-reported psychological functioning from time 1 with active CS and 3, 6, and 12 months posttreatment. For the self-report instruments, the Bonferonni correction was employed because of multiple analyses. Thus, for these analyses, the accepted P value was set at 0.003 or (0.05/21).

Symptom Checklist 90R: In general, for these subscales, symptoms fell from pretreatment to 3 months postoperatively and then further declined at 6 months, as noted by the linear and quadratic trends (see Table 2 and Fig. 1). There were significant changes across time in the following subscales of the SCL-90R: obsessive-compulsive, depression, anxiety, paranoia, psychotic, general severity, and positive symptom distress. Changes in symptoms of the following subscales were not significant after the Bonferonni correction was employed: somatization, interpersonal sensitivity, hostility, phobia, and positive symptom total.

POMS: Similar to the SCL-90R scores, there were significant changes across time in the tension-anxiety and confusion subscales of the POMS (see Table 3). No significant trends across time were noted after Bonferonni correction for depression-dejection, anger-hostility, vigor, fatigue, or total mood score.

State-Trait Anxiety Inventory: There were no significant changes across time for state ($P = 0.07$) or trait anxiety ($P = 0.12$; see Table 4).

Is psychological functioning after treatment for CS related to recovery of the HPA axis?

ACTH stimulation tests were performed in those patients with pituitary adenoma resection or an ectopic source. The frequencies of a normal cortisol response (NRM) of 18 μg/dL or more and an abnormal cortisol response (ABN) of less than 18 μg/dL to the ACTH stimulation test were as follows: 3

TABLE 1. Medical information and psychological diagnoses in patients with Cushing's syndrome before and after treatment

Patient no.	Diagnosis	Treatment	Before Cushing's	During Cushing's	Pre-Tx interview	3 Months post-Tx	3 Months response	6 Months post-Tx	6 Months response	12 Months post-Tx	12 Months response
1	CD	Rx, RADS	MA	HMA, MDD PAN	HMA, ADD						
2	CD	BADx, RADS			ADD			—		—	
3	CD	TSS					ABN	ADD	ABN	ADD	NRM
4	AA	UADX			ADD	ADD	ABN	ADD	ABN	MDD	ABN
5	EC	BADX		MDD	MDD, ADD	MDD, ADD SUICDL		ADD		ADD	
6	CD	TSS		MDD, PAN MELANC		MDD, PAN	ABN		ABN		NRM
7	CD	—		MIN DEP	MIN DEP ADD	—		—		—	
8	CD	Rx, RADS	ETOH			MDD					ABN
9	CD	TSS				PAN AGORA	ABN		ABN		NRM
10	CD	TSS					ABN		NRM		NRM
11	EC	THRx			ADD		ABN		ABN		ABN
12	CD	TSS		MDD		MDD	ABN	MDD, ADD DRUG SUICDL	ABN	MDD, ADD SUICDL	ABN
13	CD	TSS		MIN DEP INT DEP	INT DEP ADD	SUICDL	NRM	ADD	ABN		NRM
14	CD	TSS				MDD, ADD	ABN	—	ABN		ABN
15	CD	TSS				MDD	ABN	MDD, ADD	ABN		ABN
16	CD	TSS	SIM PHB	MDD	ADD	ADD	ABN		ABN		NRM
17	CD	BADx, RADS				—		—		—	
18	EC	THRx	DRUG		ADD		NRM		NRM		NRM
19	CD	TSS		MDD		—		—		—	
20	CD	BADx		MDD	MDD, ADD			—			
21	CD	TSS	MDD		ADD		NRM		NRM		NRM
22	CD	TSS		MDD MELANC	MDD	ADD	ABN	ADD	ABN		ABN
23	CD	TSS	DRUG PAN		ADD	—	—		ABN	ADD	ABN
24	CD	TSS		MDD MELANC			ABN		ABN		NRM
25	CD	TSS		MDD	MDD, ADD		ABN		ABN		ABN
26	CD	TSS		HMA PAN	HMA, ADD PAN	MDD	ABN		ABN		ABN
27	CD	TSS				MDD SUICDL	ABN	MDD	ABN		NRM
28	CD	TSS		ETOH DRUG	ADD, ETOH DRUG	ADD	ABN	ADD DRUG	NRM	DRUG	
29	CD	TSS					ABN		ABN		ABN
30	CD	TSS			ADD	MDD, ADD	ABN		ABN	ADD	ABN
31	CD	TSS		MDD	ADD		ABN		NRM		NRM
32	CD	TSS				—		—			NRM
33	CD	BADx						—			

Diagnosis: origin of Cushing's syndrome (CD, Cushing's disease, pituitary; AA, adrenal adenoma; EC, ectopic). Treatment: Rx, medication; RADS, irradiation; TSS, transsphenoidal surgery; BADx, bilateral adrenalectomy; UADx, unilateral adrenalectomy; THRx, thoracotomy. Before Cushing's; psychopathology before any signs of Cushing's syndrome. During Cushing's; psychopathology with Cushing's syndrome, at any time. Pre-Tx interview: psychopathology at first interview before therapy. 3, 6, and 12 month responses: cortisol response to ACTH stimulation test (ABN, abnormal response, cortisol <18; NRM, normal response, cortisol ≥18). Psychiatric diagnosis: MA, Mania; PAN, panic; SUICDL, suicidal; MELANC, melancholic; DRUG, drug abuse; AGORA, agoraphobia; —, no return visit; HMA, hypomania; MDD, major depressive disorder; ADD, atypical depression; MIN DEP, minor depression; ETOH, alcohol abuse; INT DEP, intermittent depression; Blank, no diagnosis.

months: NRM, 3 (13.6%); ABN, 19 (86.4%); 6 months: NRM, 5 (21.7%); ABN, 18 (78.3); and 12 months: NRM, 12 (50%); ABN, 12 (50%). Thus, the number of patients with HPA axis recovery increased across time.

Spearman's ρ correlations were computed to determine the concurrent relations between recovery of the HPA axis (NRM/ABN response) and 1) the presence or absence of a psychiatric diagnosis, and 2) the level of psychological functioning from self-report questionnaires 3, 6, and 12 months after correction of hypercortisolism. There were no significant ($P > 0.05$) correlations after the Bonferonni correction of the HPA axis response with the diagnosis of atypical depression or any diagnosis from the SADS-LA or for the self-report measures.

Fisher's exact tests were computed to determine whether having a psychiatric diagnosis after correction of

TABLE 2. Means and SD of subscale scores from the SCL-90R for the longitudinal sample (n = 21) of patients with Cushing's syndrome

	Time 1	3 Months	6 Months	12 Months	Overall F	*P*	Trends F	*P*
Somatization	63.86	57.52	56.10	59.05	3.18	0.049	lin 4.4	0.048
	(7.12)	(9.46)	(9.48)	(9.11)			quad 7.9	0.011
Obsessive-compulsive	65.29	57.33	54.86	56.00	6.95	0.003	lin 17.5	<0.001
	(9.73)	(13.37)	(11.47)	(13.68)			quad 8.79	0.008
Interpersonal sensitivity	64.00	54.29	54.00	54.05	6.41	0.004	lin 16.04	0.001
	(9.11)	(10.61)	(13.00)	(12.90)			quad 14.16	0.001
Depression	66.33	58.76	55.67	55.48	6.92	0.003	lin 17.69	<0.001
	(7.84)	(10.31)	(12.87)	(13.77)			quad 19.73	<0.001
Anxiety	65.00	52.38	52.95	53.67	9.03	0.001	lin 21.28	<0.001
	(10.25)	(11.82)	(10.89)	(12.78)			quad 19.73	<0.001
Hostility	58.71	50.57	51.95	51.57	4.35	0.018	lin 9.64	0.006
	(8.70)	(8.38)	(9.75)	(10.15)			quad 7.33	0.014
Phobia	56.43	53.10	48.57	51.14	5.69	0.006	lin 13.36	0.002
	(9.48)	(8.39)	(7.17)	(7.58)			quad 4.40	0.049
Paranoid	56.00	46.76	50.95	50.00	7.84	0.001	lin 4.77	0.041
	(11.02)	(8.28)	(10.18)	(11.08)			quad 5.97	0.024
Psychotic	67.86	56.19	57.33	53.95	13.15	0.001	lin 34.68	<0.001
	(5.76)	(10.09)	(9.60)	(9.67)			quad 9.70	0.005
							cub 5.86	0.025
General severity	66.52	56.62	54.67	55.24	8.55	0.001	lin 25.22	<0.001
	(7.71)	(10.51)	(12.75)	(12.48)			quad 15.07	0.001
Positive symptom distress	63.14	57.05	54.52	57.05	7.31	0.002	lin 8.92	0.007
	(7.74)	(8.76)	(10.43)	(7.85)			quad 14.48	0.001
Positive symptom total	64.38	55.10	53.91	54.19	5.77	0.006	lin 16.25	0.001
	(7.93)	(10.16)	(13.09)	(12.79)			quad 11.83	0.003

lin, Linear; quad, quadratic.

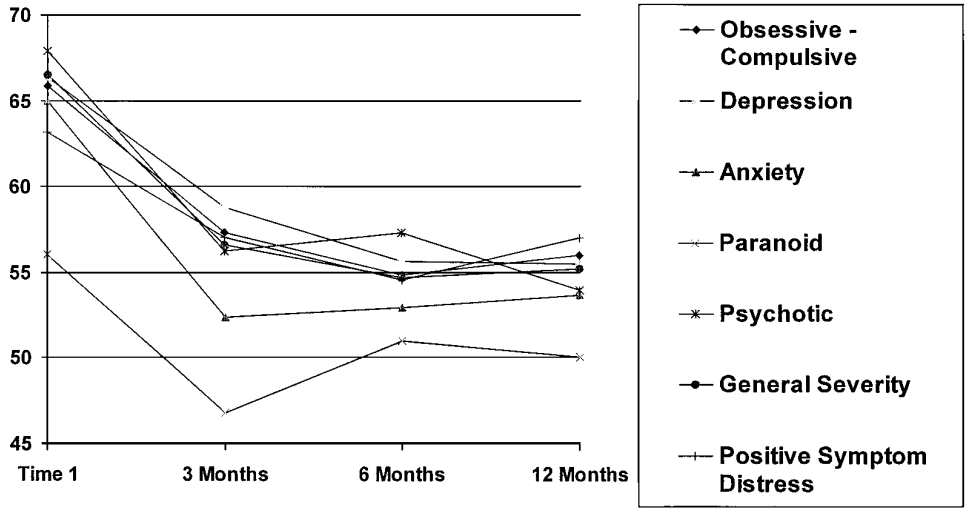

FIG. 1. Significant changes in mean T scores of subscales of the Symptom Checklist-90R for patients with CS during CS (time 1) and 3, 6, and 12 months posttreatment.

hypercortisolism was independent from recovery of the HPA axis. All tests were nonsignificant ($P > 0.05$), showing independence between psychiatric diagnoses after correction of hypercortisolism and HPA axis recovery. To further examine whether psychological functioning was related to HPA axis recovery, we used the latter as a covariate in the above repeated measures ANOVA for the self-report measures. The covariate was not significant for any of these analyses, indicating that the change in measures of psychopathology was independent of the HPA axis response.

Next, we examined the relationship between self-report measures of psychopathology and concentrations of cortisol at 0 (baseline), 30, and 60 min after the morning ACTH stimulation test. No significant relations were noted 3 months after correction of hypercortisolism. Six and 12 months after correction of hypercortisolism, lower morning baseline concentrations of cortisol were related to higher numbers of symptoms on many of the subscales of the SCL-90R (see Table 5). Few correlations were evident with self-report measures and the cortisol concentration measured at 30 or 60 min. Six months after correction of hypercortisolism for the POMS, patients reporting more vigor had higher concentrations of cortisol at baseline (r = 0.66; $P = 0.001$), 30 min (r = 0.58; $P = 0.005$), and 60 min (r = 0.66; $P = 0.001$). Similarly, 12 months after correction of hypercortisolism, the correlations were r = 0.57 ($P = 0.008$) at baseline and r = 0.47 ($P = 0.045$) at 30 min. No significant correlations were noted with the Hamilton score 3, 6, or 12 months after correction of hypercortisolism.

TABLE 3. Means and SDs of subscale scores from the POMS for the longitudinal sample of patients with Cushing's syndrome

	Time 1	3 Months	6 Months	12 Months	Overall F	*P*	Trends F	*P*
Tension/anxiety	13.94 (8.74)	7.53 (6.27)	6.88 (6.54)	9.41 (9.52)	7.79	0.003	quad 20.61	≤0.001
Depression/dejection	13.24 (10.08)	7.59 (9.27)	7.29 (10.45)	7.82 (9.19)	2.79	0.079		
Anger/hostility	8.18 (9.12)	3.18 (4.50)	4.77 (7.81)	6.00 (9.73)	3.50	0.044	quad 9.0	0.008
Vigor	10.18 (7.74)	10.53 (4.77)	11.77 (6.06)	13.77 (7.81)	1.99	0.162		
Fatigue/inertia	11.53 (8.65)	9.29 (8.10)	7.59 (6.81)	7.88 (7.85)	2.56	0.097		
Confusion/bewilderment	9.82 (4.92)	7.59 (5.06)	5.06 (3.03)	6.59 (6.43)	9.05	0.001	lin 13.39	0.002
							quad 7.51	0.014
Total mood disorder	46.53 (37.79)	24.65 (30.19)	19.82 (33.42)	23.94 (43.96)	5.86	0.008	lin 7.72	0.013
							quad 9.04	0.008

lin, Linear; quad, quadratic.

TABLE 4. Means (SD) of the Hamilton Depression Rating Scale and the State Trait Anxiety Scale (STAI) in the longitudinal sample of patients with Cushing's syndrome

Measure	Time 1	3 Months	6 Months	12 Months
Hamilton	7.32 (5.58)	7.14 (6.54)	5.68 (6.27)	5.05 (7.32)
STAI state	60.09 (13.02)	55.04 (13.08)	53.09 (13.73)	52.26 (13.73)
STAI trait	63.09 (14.41)	57.55 (13.03)	57.96 (13.29)	55.50 (11.89)

TABLE 5. Pearson correlation coefficients of the SCL-90R with cortisol response to ACTH stimulation test in patients with Cushing's syndrome (posttreatment)

Cortisol	6 months		12 months	
	0 min	60 min	0 min	60 min
Somatization	−0.59[a]		−0.45[b]	
Obsessive-compulsive	−0.56[b]		−0.43[b]	
Interpersonal sensitivity	−0.51[b]			
Depression	−0.55[b]	−0.46[b]		
Anxiety	−0.51[b]			
Hostility	−0.51[b]	−0.42[b]		
Phobia				
Paranoid ideation				
Psychoticism	−0.45[b]			
General severity	−0.59[a]	−0.46[b]	−0.53[b]	
Positive symptom distress	−0.43[b]	−0.46[b]		
Positive symptom total	−0.59[a]		−0.53[a]	

[a] $P \leq 0.01$.
[b] $P \leq 0.05$.

Does having a psychiatric history before CS or having a longer duration of CS place one at risk for more psychopathology posttreatment for CS?

Spearman's ρ correlations were computed to determine the relationship between having a diagnosis of atypical depression or any other psychiatric diagnosis after correction of hypercortisolism with having either 1) a psychiatric diagnosis before the reporting of any symptoms of CS or 2) symptoms during CS. No significant correlations were noted. The duration of CS was positively related to numerous subscales on the SCL-90R, the POMS, and the Hamilton scale. Significance ranged from $P = 0.042$ to 0.004. However, to remain significant after the Bonferonni correction, a significance level of $P = 0.003$ would have had to be reached.

Discussion

It is clear that significant psychopathology remains after remission of hypercortisolism in CS and even after recovery of the HPA axis by conventional criteria. Our findings regarding postcorrection frequency of psychiatric disorders may be conservative, given that some of our patients were receiving psychotherapy and/or pharmacotherapy. Similar to the active phase of CS, the most frequent psychopathology exhibited after treatment was that of atypical depression (6). In our patients, the incidence of atypical depression progressively decreased after correction of hypercortisolism. However, the predominant finding of atypical depression supports earlier reports of low CRH in patients with CS (10), and our hypothesis that low CRH may contribute to atypical depression (9). Patients are eucortisolemic during their entire postoperative course because they are exogenously replaced with glucocorticoids. However, the CRH neuron appears to be the last part of the HPA axis to normalize (17). Although this suggests that it is CRH rather than cortisol that is responsible for the maintenance of atypical depression after correction of hypercortisolism, this is not a proven fact. We did not measure cerebrospinal fluid CRH in this study. Earlier studies indicate that serial samples of cerebrospinal fluid CRH may provide more meaningful information than a single sample (30). Atypical depression in this condition may also be related to a number of other biological or psychosocial factors yet unexplored.

Along with atypical depression in our sample, there was a decrease in the majority of symptoms of distress reported by patients in the self-report checklists, but not representing psychiatric diagnostic criteria. Such findings indicate that symptoms at levels below those of diagnostic criteria may be changing as well in the period after correction of hypercortisolism. We were conservative in our interpretation of these group differences by using the Bonferonni correction in our statistical analyses. Thus, additional group differences are plausible.

Comorbidity was evident in many of the patients during active CS as well as after remission of hypercortisolism. Comorbid conditions included panic and suicidal ideation, even at their follow-up visits, and thus obviously should not be ignored. Although only two patients met diagnostic cri-

teria for panic disorder after treatment, several others reported panic attacks or symptoms of panic that did not reach the diagnostic threshold, yet were alarming to the patients. The emergence of panic anxiety in patients cured of the disorder may result from the relative glucocorticoid deficiency of these patients, which probably allows unrestrained increases in catecholamines (31). The nonhuman primate literature shows that plasma concentrations of norepinephrine are augmented by glucocorticoid deficiency during stress, indicating that the sympathetic system is not properly restrained by glucocorticoids in these animals (32).

Panic, suicidal ideation, and depression should provide a warning to those caring for patients with CS. Patients and family members should be given information that psychopathology may persist into the postoperative period or new psychopathology may emerge. Patients are often informed that they are cured after the surgery has been completed; yet they should be informed that "cure" from a quality of life or psychological perspective may take additional months. This is evidenced by the reporting of as many as 6 patients who saw a therapist on a routine basis and by the fact that psychological intervention was recommended to as many as 12 patients after remission of hypercortisolism, including 2 who required psychiatric hospitalization.

The pattern is puzzling regarding the presence or absence of a psychiatric diagnosis across the longitudinal study. Our findings reveal that a psychiatric diagnosis that was premorbid or concurrent with CS did not influence the incidence of psychopathology after correction of hypercortisolism. Importantly, of the 29 patients with follow-up data, 4 (~14%) only had psychiatric diagnoses after treatment, which may indicate that the return of the HPA axis to normal may itself be unveiling or triggering psychopathological manifestations not precipitated previously by hypercortisolism and *vice versa*. Others reported that postoperative depression was a predictor of both nonremission and relapse after pituitary surgery of Cushing's disease (33). This makes sense and is compatible with our data, but is of limited value.

Our findings also revealed that having a psychiatric diagnosis after cure of CS was not strictly related to recovery of the HPA axis. As anticipated, recovery of the HPA axis did increase from 13.6% of the patients at 3 months posttreatment to 54.6% at 12 months posttreatment, numbers comparable to our earlier findings (17, 34). During this time there was a parallel decrease in the presence of psychiatric diagnoses. Although HPA axis recovery from an endocrine perspective is considered at a cortisol response of 18 μg/dL anytime during the rapid ACTH stimulation test, psychological recovery may not fit that same criterion. Importantly, when we examined the relationship of the concentration of cortisol rather than an all or none response, we did find a relationship. Lower morning baseline concentrations of cortisol were related to more psychopathology, as reported by the patients on the SCL-90R and POMS, particularly 6 and 12 months after correction of hypercortisolism. This relationship was not apparent 3 months after correction of hypercortisolism, presumably when concentrations of cortisol were generally too low to allow a proper correlation. This suggests that the spontaneous secretory activity of the CRH neuron may be a more important psychological determinant.

Certainly, the psychological recovery of cured patients with CS is multifactorial from both a neuroendocrine and a psychosocial perspective. Sonino and colleagues (35) recently reported that more stressful life events may play a causal role in the expression of depression in pituitary-dependent Cushing's disease. This is compatible with our idea that hypercortisolism or hypocortisolism, and hence altered secretion of hypothalamic CRH, increase the vulnerabilities of an individual to stressors and, in turn, the expression of depression in response to such stressors.

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