

Factitious Cushing Syndrome*

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ABSTRACT

There have been few reports of factitious Cushing syndrome. To characterize the clinical and laboratory features leading to this unusual diagnosis, we describe 6 patients (5 women, 1 man), ages 31–44, identified retrospectively among 860 patients evaluated for hypercortisolism at the National Institutes of Health Clinical Center.

All six patients had multiple surgeries unrelated to Cushing syndrome and a history of depression or anxiety. Four patients had close contact with the medical profession, three a history of drug abuse, and three had undergone previous treatment for Cushing syndrome. The physical features of Cushing syndrome were variable and not helpful in the differential diagnosis with endogenous Cushing syndrome. Four patients had striking variability in urine-free cortisol (UFC) and 17-hydroxysteroid (17-OHCS) values from low to high. Adrenal com-

puted tomography, performed in two patients, showed small adrenal glands ($n = 1$) or a left-sided mass ($n = 1$), and adrenal magnetic resonance imaging, performed in one patient, showed atrophic glands. Pituitary magnetic resonance imaging, carried out in four patients, was either normal ($n = 1$) or exhibited questionable signs of microadenoma ($n = 3$). Determination of synthetic glucocorticoids by high pressure liquid chromatography (HPLC) was positive in the four patients in whom it was performed.

Factitious Cushing syndrome is a difficult diagnosis. To conserve time and resources, high pressure liquid chromatography analysis of urine steroids, the most definitive test for the factitious disorder, should be performed whenever there is clinical suspicion of glucocorticoid abuse. (*J Clin Endocrinol Metab* 81: 3573–3577, 1996)

THE Munchausen syndrome is a chronic factitious disorder characterized by the intentional production of physical or psychological signs or symptoms, with the motivation to assume the sick role and without external incentives for the behavior (1, 2).

In the context of this syndrome, the surreptitious administration of several hormones has been reported. For example, insulin administration, leading to hypoglycemia and thus mimicking insulinoma, thyroid hormone administration mimicking thyrotoxicosis, and catecholamine intake imitating pheochromocytoma, have all been described (3–5).

By contrast, despite the widespread medical use of glucocorticoids, reports of the factitious administration of these hormones have been uncommon (6–10).

We report here six patients with factitious Cushing syndrome who presented for evaluation of hypercortisolism at the National Institutes of Health (NIH) Clinical Center during the past 15 years.

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Materials and Methods

Patients

The 6 patients with a diagnosis of factitious Cushing syndrome, from among the 860 patients referred for hypercortisolism to the NIH Clinical Center over the last 15 years, were reviewed (Table 1).

Tests

The outcome measures included urinary cortisol and 17-hydroxysteroid (17-OHCS) excretion, diurnal rhythm of plasma cortisol, plasma ACTH, high-pressure liquid chromatography (HPLC) determinations of synthetic glucocorticoids in plasma and urine, adrenal size by computed tomography (CT) and magnetic resonance imaging (MRI) scan, and the presence or absence of pituitary microadenoma by MRI scan. Additionally, some patients received tests for secondary adrenal insufficiency (short ACTH test; ref.11), for differentiation of pituitary vs. ectopic causes of Cushing syndrome (6-day dexamethasone suppression test (12), and CRH test (13).

Assays

The HPLC determinations were performed at the Mayo Clinic using a commercially available procedure (Rochester, MN). Other measurements were performed as previously described (12).

Results

Patient A

Patient A, a 37-yr-old woman, was originally evaluated for vertebral compression fractures. Past medical history included exploratory laparotomy, laparoscopic tubal ligation, hysterectomy, and bilateral arthroscopic surgery. She had worked previously as a medical secretary. She was separated

TABLE 1. Characteristics of patients with factitious Cushing syndrome

Patient	Age (yr)	Sex	Marital status	Occupation	Close contact with medical profession (patient or family members)	Psychiatric symptoms	Drug abuse	Previous treatment for Cushing syndrome	Multiple surgeries unrelated to Cushing syndrome
A	37	F	Separated	Medical secretary	Yes	Depression	No	No	Yes
B	31	M	Married	Mortician	No	Anxiety	Yes	TSS	Yes
C	44	F	Married	Housewife	No	Depression	No	TSS	Yes
D	32	F	Divorced	Contract administrator	Yes	Depression	Yes	No	Yes
E	36	F	Divorced	Nurse	Yes	Threat to commit suicide	No	ADX, TSS, IRR	Yes
F	31	F	Single	Dietitian	Yes	Anxiety Insomnia	Yes	No	Yes

F, female; M, male; ADX, Adrenalectomy; IRR, Pituitary Irradiation; TSS, Transsphenoidal Surgery.

TABLE 2. Serial measurements of basal 24-h urine cortisol, 17-OHCS, and creatinine in Patient A

Date	UFC ($\mu\text{g}/\text{day}$)	17-OHCS (mg/day)	Urine creatinine (gm/day)
8/16	5,282	28.2	1.41
8/18	3,323	16.5	1.03
8/19	48	1.3	1.12
8/20	10	1.3	0.92
8/21	10	0.7	1.1
8/22	13	2.8	1.0
8/23	623	6.4	0.9
8/24	1597	6.6	1.03
8/25	18	0.7	1.05

from her alcoholic husband. The 24-h urine free cortisol (UFC) was elevated (99, 155, 140, 200 $\mu\text{g}/\text{day}$, normal 20–90). A low-dose dexamethasone suppression test (2 mg/day) showed a paradoxical rise (UFC: baseline, 37 $\mu\text{g}/\text{day}$; second day of dexamethasone, 181 $\mu\text{g}/\text{day}$). During her first admission to NIH, UFC and urine 17-OHCS levels ranged from low to high and were suppressed after low-dose dexameth-

asone. Diurnal rhythm of plasma cortisol was preserved, although the evening values were elevated (20.3 $\mu\text{g}/\text{dL}$ in the morning, 9.4 $\mu\text{g}/\text{dL}$ at midnight). ACTH and cortisol were slightly elevated and did not respond to CRH. An MRI of the pituitary suggested a left-sided microadenoma. CT scan showed normal adrenals. She was discharged with the diagnosis of possible periodic Cushing syndrome.

The patient was readmitted 11 months later with increasing bone pain and depression. She asked numerous staff members what results were expected for her endocrine tests. Measurements of ACTH and cortisol every 30 min for 24 h yielded low values indicating secondary adrenal insufficiency. UFC and 17-OHCS alternated abruptly between very high and very low values (Table 2). A short ACTH test showed a suppressed response (peak cortisol 12.7 $\mu\text{g}/\text{dL}$, normal $\geq 18 \mu\text{g}/\text{dL}$). A repeat adrenal CT showed decreased adrenal size compared with the original admission (Fig. 1).

Five months later the UFC was markedly elevated (3,000 $\mu\text{g}/\text{day}$), but subsequent plasma cortisol levels were less than 5 $\mu\text{g}/\text{dL}$ on four consecutive days. Dexamethasone and

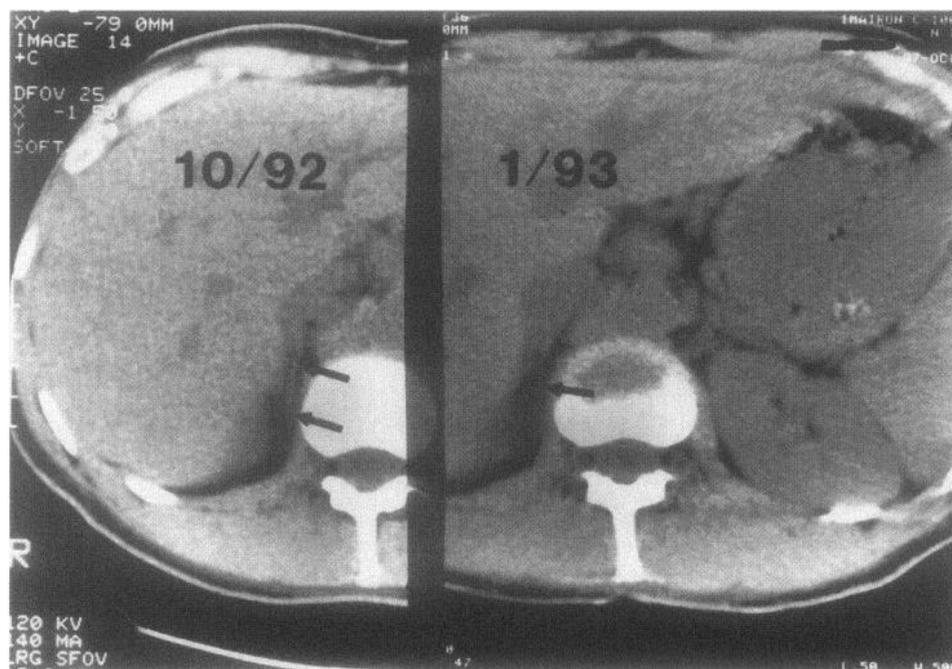


FIG. 1. Comparison of adrenal size over time by CT. The arrows indicate the medial limb of the right adrenal gland that shows appreciable narrowing from 10/92 to 1/93 (Patient A).

prednisolone were detected by HPLC in her blood and urine. Neither had been prescribed. The patient was confronted with the evidence that her elevated steroids did not result from endogenous production. She denied using steroids, but did not question the diagnosis. She was observed in the hospital for two days to exclude psychiatric instability, and was then discharged, with recommendations regarding therapy for adrenal insufficiency and for psychiatric follow-up.

Patient B

Patient B was a 31-yr-old man who had undergone transsphenoidal surgery for Cushing's disease. At initial evaluation the UFC had increased paradoxically during a low-dose dexamethasone test. An MRI was interpreted as indicating a pituitary microadenoma. Transsphenoidal surgery was performed but the pathological report did not confirm a microadenoma. After surgery, cortisol levels dropped to 2 $\mu\text{g}/\text{dL}$. The patient was discharged on cortisone acetate 37.5 mg/day.

Nine months after discontinuing cortisone acetate, UFC was elevated (360 and 148 $\mu\text{g}/\text{day}$), and the patient was referred to NIH. Past medical history included cocaine and iv drug abuse, exploratory laparotomy for severe abdominal pain, several laminectomies, bilateral hernia repairs, and repair of a perineal fistula. The patient had recently moved, had changed his name, had married, and was studying to become a mortician. The physical examination was consistent with Cushing syndrome.

Plasma cortisol levels were persistently elevated (36.3 $\mu\text{g}/\text{dL}$ in the morning, 32.5 $\mu\text{g}/\text{dL}$ at midnight). Plasma ACTH was suppressed and did not respond to CRH. UFC and 17-OHCS showed alternation of very high and modestly elevated levels (UFC: 124 up to 9,016 $\mu\text{g}/\text{day}$; 17-OHCS: 26.8 up to 192.5 mg/day, normal 2–6). A dexamethasone suppression test showed no suppression of UFC at the high dose (UFC: 327 $\mu\text{g}/\text{day}$). An MRI of the pituitary showed no definite tumor. The adrenal glands were atrophic by MRI.

The differential diagnosis included micronodular adrenal disease *vs.* factitious Cushing syndrome. The patient denied taking steroids. At exploratory laparotomy, no pigmented adrenal nodules were found; both glands were atrophic. Later a computer print-out from a local pharmacy, provided by the patient's wife, showed multiple prescriptions for cortisone acetate. He was discharged to the care of his referring physician. He subsequently contacted the psychiatrist at NIH, admitted that he had been taking steroids, and was referred to a local psychiatrist.

Patient C

Patient C was a 44-yr-old woman who had presented 3 yr earlier with a 50-kg weight gain, depression, fatigue, and bone pain. Family history included an aunt with Cushing syndrome. The UFC was twice the upper normal limit, but there were no classical signs of Cushing syndrome.

Periodic measurements of UFC gradually rose to 240 $\mu\text{g}/\text{day}$. Plasma ACTH ranged from 25 to 40 pg/mL (normal 7–51). Transsphenoidal exploration and hemihypophysectomy at an outside center were unsuccessful, and no tumor

was found. Post-operatively, the UFC remained elevated (127 to 452 $\mu\text{g}/\text{day}$).

Upon admission to NIH the only sign of Cushing syndrome was central obesity. Cortisol diurnal rhythm was normal (8.9 $\mu\text{g}/\text{dL}$ in the morning, 3.0 $\mu\text{g}/\text{dL}$ at midnight). A CRH test showed a normal plasma cortisol response (baseline, 4.5 $\mu\text{g}/\text{dL}$; peak, 15.9 $\mu\text{g}/\text{dL}$). Urine 17-OHCS was normal or slightly elevated (up to 6.8 mg/day, normal 2–6). Simultaneous UFC was less than 1 $\mu\text{g}/\text{day}$, and plasma DHEA-S was low (0.2 $\mu\text{g}/\text{mL}$, normal 0.6–2.9). A second diurnal cortisol showed suppressed values (3.3 $\mu\text{g}/\text{dL}$ in the morning, 1.2 $\mu\text{g}/\text{dL}$ at midnight). Pituitary MRI showed a questionable lesion. Adrenal glands were normal by CT. Psychological evaluation suggested depression.

The suspicion of factitious Cushing syndrome led to HPLC analysis of urine, which revealed synthetic steroids (Fig. 2). Her physicians then explained that the evidence excluded endogenous production of steroids and indicated an exogenous source. She commented that she was glad she did not have "true" Cushing syndrome, denied adamantly taking steroids, and declined further psychiatric consultation. She was returned to the care of her referring physician.

Patient D

Patient D was a 32-yr-old woman who presented with florid Cushing syndrome. Past medical history included ap-

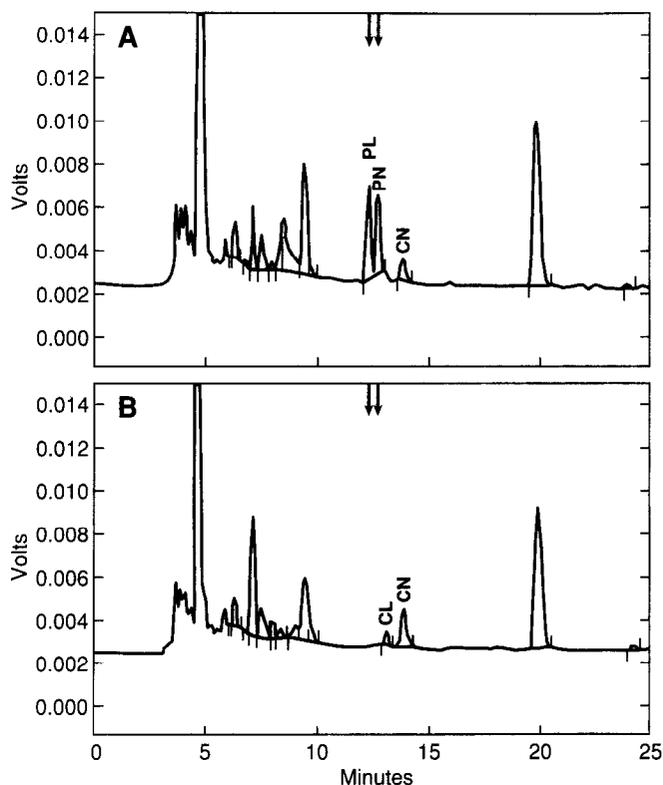


FIG. 2. HPLC determinations of synthetic steroids in the urine in patient C. The determinations, made four weeks apart, are shown in panels A and B. Prednisolone (PL) and prednisone (PN) are present in panel A (arrows). In the same specimen, cortisol (CL) is suppressed at < 1.0 ng/mL, and cortisone (CN) is low (23 ng/mL). Note the disappearance of prednisone and prednisolone, and the increase of cortisol and cortisone in panel B.

TABLE 3. Weekly measurements of basal 24-h urine cortisol and 17-OHCS and of plasma cortisol in Patient D

Date	UFC ($\mu\text{g/day}$)	17-OHCS (mg/day)	Plasma cortisol ($\mu\text{g/dL}$)
08/17	157	12.6	12.3
08/24	< 10	0.8	14.2
08/31	< 10	0.5	11.7
09/07	11,888	26.3	11.9

pendectomy and herniated lumbar disc. The patient's father was an alcoholic. Her mother, who was a nurse, had a history of depression. The patient had abused alcohol, marijuana, and cocaine. She claimed to have worked in the diplomatic corp in Turkey and France, which turned out to be untrue. At initial evaluation serum cortisol was $1.5 \mu\text{g/dL}$, and UFC was normal. Subsequent values of UFC were 155, 62, and $128 \mu\text{g/day}$, with serum cortisol of 13, 22, and $11 \mu\text{g/dL}$, respectively. Low-dose dexamethasone suppressed the serum cortisol ($0.4 \mu\text{g/dL}$) but not the UFC ($600 \mu\text{g/day}$). After high-dose dexamethasone, UFC was $102 \mu\text{g/day}$ and serum cortisol undetectable. Pituitary MRI showed a possible tumor. The adrenal glands were small by CT.

Upon admission to NIH plasma cortisol values were low normal ($7.5 \mu\text{g/dL}$ in the morning, $\leq 1 \mu\text{g/dL}$ at midnight). Plasma potassium was low (2.8 meq/L), and a urine sample tested positive for chlorothiazide. The patient denied taking diuretics, but her family doctor described repeated diuretic prescriptions. Psychiatric evaluation revealed anxiety and depression. The patient was discharged with the diagnosis of factitious *vs.* periodic Cushing syndrome and was asked to perform periodic urine collection (Table 3). One month later, plasma DHEAS was suppressed ($0.1 \mu\text{g/mL}$, normal 0.6 – 2.9). A markedly elevated UFC value ($11,888 \mu\text{g/day}$) was observed after explaining to the patient that pituitary surgery could be not considered when her UFC was low. After being confronted by the medical team, she denied taking glucocorticoids and elected to be followed by her local physician.

Patient E

Patient E was a 36-yr-old woman who was reluctant to provide the names of her past physicians. Later, she admitted giving a false history to impede contact with her previous doctors. The past medical history included intermittent flank pain, three exploratory laparotomies, cholecystectomy, cecal volvulus, and nasal surgery. The patient had worked as a nurse but was currently unemployed. At physical examination, she was an obese Cushingoid woman who smiled inappropriately, while describing intense pain.

The correct story was eventually reconstructed by locating her previous physicians. When the diagnosis of Cushing syndrome was first considered, she urgently requested adrenalectomy. CT of her adrenals revealed a left-sided mass, and she underwent left adrenalectomy. She then referred herself to another hospital, where she underwent transsphenoidal surgery. No pathological evidence of pituitary adenoma was found, but symptoms improved. Subsequently, she sought help at another center, where urine prednisolone was detected by HPLC. When confronted, the patient left and was lost to follow-up.

During admission to NIH, plasma ACTH and cortisol, and urine 17-OHCS and cortisol were undetectable. These findings prompted our solicitation of the above history and the diagnosis of factitious Cushing syndrome. After confrontation, she threatened suicide. She was returned to the care of her local physicians.

Patient F

Patient F was a 31-yr-old woman who presented to an endocrinologist with a recent 20-kg weight gain, back pain, muscular weakness, hirsutism, insomnia, and anxiety. Past medical history included sexual abuse, depression, narcotic addiction, and several laparotomies for abdominal pain. The patient was an unemployed dietician, whose sister was a nurse. Physical examination revealed signs of florid Cushing syndrome. Plasma ACTH (2 pg/mL , normal 7 – 51), plasma cortisol ($0.4 \mu\text{g/dL}$, normal 2 – 13), and UFC ($5 \mu\text{g/day}$, normal 20 – 90) were suppressed. Pituitary MRI was normal, but adrenal CT revealed cortical atrophy.

The patient denied steroid use; however, prednisone (27 and $29 \mu\text{g/day}$) was found in 2 of 3 urine samples analyzed by HPLC, while plasma cortisol was consistently undetectable. These data were discussed with her referring endocrinologist, who resumed the patient's medical management.

Discussion

We report here 6 patients with factitious Cushing syndrome, who were identified retrospectively among 860 patients who were evaluated for hypercortisolism at the NIH Clinical Center. HPLC analysis of urine for synthetic steroids confirmed the diagnosis in 4 of the 6 patients. The other 2 patients were diagnosed because of the pattern of suppression of ACTH and either marked variability or suppression of urine cortisol levels.

The diagnosis of factitious Cushing syndrome was often difficult. The differential diagnosis includes periodic Cushing syndrome, in which there is intermittent hypersecretion of glucocorticoids followed by normal or low values (14). However, whereas periodic Cushing syndrome has a cycle length of at least 5 days, factitious Cushing syndrome may exhibit highly elevated cortisol values one day followed by low levels the next, as was the case in our patients A, B, and D.

The history provided important clues to the factitious etiology. Similar to what has usually been reported in patients with Munchausen syndrome, four patients had access to the medical profession through employment, family members, or friends, and all had gone through multiple prior surgeries for unrelated illnesses. By contrast, the physical findings were indistinguishable from those of patients with endogenous Cushing syndrome and were therefore not helpful in differential diagnosis. Similarly, the psychiatric symptoms in our patients were of limited usefulness in differential diagnosis because of the high prevalence of psychiatric symptoms in nonfactitious Cushing syndrome.

Differently from Cushing syndrome, in which UFC and 17-OHCS are usually persistently elevated, the rapid alternation in patients A, C, and D from very low to very high values raised suspicion of a factitious etiology. A discrepancy

between plasma and urine glucocorticoid levels, as occurred in patient D, also indicated factitious disease. Additionally the presence of atrophic adrenal glands, as noted in patients A, B, D, and F, should have raised suspicion of a factitious etiology.

Synthetic glucocorticoids were detected by HPLC in the four patients in whom HPLC was performed. This inexpensive procedure was the most specific test of the factitious nature of the disorder. We recommend that it be performed whenever there is a clinical suspicion of factitious Cushing syndrome.

Pituitary MRI may be misleading, since 10–15% of normal people have abnormal findings, termed “incidentalomas”, that are not associated with endocrine abnormalities (15). Such unrelated pituitary findings apparently contributed to previous transphenoidal surgery in three of our patients.

Diurnal rhythm of cortisol has an important role in confirming the presence of Cushing syndrome (16), and the possibility of factitious or periodic Cushing syndrome is suggested when the physical evidence of Cushing syndrome is accompanied by suppressed plasma ACTH and cortisol levels.

The complete recovery of the suppressed HPA axis usually takes about 1 yr after surgical cure of endogenous hypercortisolism (17, 18). Thus, once the surreptitious nature of Cushing syndrome is proven, sudden withdrawal of glucocorticoids should be avoided. The patient should be considered at risk for adrenal insufficiency and should receive instruction for the emergency treatment of this condition.

Patients with factitious disorders are at high risk for increased morbidity and mortality (19). They represent a diagnostic challenge to the physician, and perhaps even more, a challenge to the physicians’ ability to empathize with them. Future studies are needed to better understand these patients’ underlying personality disorder(s), and, whenever feasible, to assess the response to psychiatric treatment.

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