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Expert Endocrine Consult

Recognition of Nonneoplastic Hypercortisolism in the Evaluation of Patients With Cushing Syndrome

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Abstract

The evaluation of suspected hypercortisolism is one of the most challenging problems in medicine. The signs and symptoms described by Dr Harvey Cushing are common and often create diagnostic confusion to even experienced endocrinologists. Cushing syndrome is classically defined as neoplastic hypercortisolism resulting from an ACTH-secreting tumor or from autonomous secretion of excess cortisol associated with benign or malignant adrenal neoplasia. The increasing recognition of the negative cardiometabolic effects of mild cortisol excess without overt physical signs of Cushing syndrome has led to more screening for endogenous hypercortisolism in patients with adrenal nodular disease, osteoporosis, and the metabolic syndrome. However, sustained or intermittent activation of the dynamic hypothalamic-pituitary-adrenal axis caused by chemical (alcohol), inflammatory (chronic kidney disease), psychologic (major depression), and physical (starvation/chronic intense exercise) stimuli can result in clinical and/or biochemical features indistinguishable from neoplastic hypercortisolism. Nonneoplastic hypercortisolism (formerly known as pseudo-Cushing syndrome) has been recognized for more than 50 years and often causes diagnostic uncertainty. This expert consultation describes two patients with features of Cushing syndrome who were referred for inferior petrosal sinus sampling for the differential diagnosis of ACTH-dependent hypercortisolism. Both patients were discovered to have nonneoplastic hypercortisolism: one from a covert alcohol use disorder and the other to chronic kidney disease. This consultation emphasizes the value of a good history and physical examination, appropriate laboratory testing, and the desmopressin acetate stimulation test to aid in distinguishing neoplastic from nonneoplastic hypercortisolism.

Key Words: Cushing disease, ACTH, cortisol, hypothalamic-pituitary-adrenal axis, desmopressin, corticotrophs

Abbreviations: AIH, alcohol-induced hypercortisolism; CKD, chronic kidney disease; CPAP, continuous positive airway pressure; dDAVP, desmopressin acetate; DST, dexamethasone suppression test; HPA, hypothalamic-pituitary-adrenal; IPSS, inferior petrosal sinus sampling; LNSC, late-night salivary cortisol; OSA, obstructive sleep apnea; PEth, phosphatidylethanol.

The clinical appreciation and evaluation of endogenous hypercortisolism has changed significantly since Dr Harvey Cushing's 1932 monograph describing a "polyglandular syndrome" [history summarized in [1-4]]. He described a phenotype that included truncal obesity often with wide violaceous striae, prominent facial fullness with increased dorsocervical fat, muscle wasting, hirsutism, and hypogonadism. Dr Cushing speculated that this disorder was the result of a basophilic pituitary tumor associated with adrenal hyperactivity (Cushing disease). With the development of more sensitive and specific methods and laboratory tests to assess hypothalamic-pituitary-adrenal (HPA) function accompanied by refined diagnostic thresholds, the diagnosis of milder degrees of cortisol excess have been identified (referred to as subclinical or hidden hypercortisolism) [5-9]. Nonetheless, mild hypercortisolism associated with autonomous cortisol secretion from adrenal nodular disease is associated with an increased risk for cardiovascular morbidity and mortality [5, 6]. Many patients with chronic mild cortisol excess have an increased risk for hypertension, hyperglycemia, and low bone density [7-9].

Endogenous, neoplastic hypercortisolism is usually the result of a pituitary or ectopic tumor secreting ACTH or from adrenal (ACTH-independent) cortisol excess from benign or malignant adrenal nodular disease [10-13]. Nonneoplastic hypercortisolism (previously called pseudo-Cushing syndrome) has been recognized for more than 50 years and includes the alcohol use disorder, neuropsychiatric disorders, chronic kidney disease, and poorly controlled diabetes mellitus [14] (Table 1).

The clinical and biochemical features of nonneoplastic hypercortisolism are often indistinguishable from true neoplastic Cushing syndrome causing further diagnostic confusion (Table 2). As clinicians screen more patients with obesity, cardiometabolic dysfunction, low bone density, and adrenal nodules for hypercortisolism, the problem of nonneoplastic hypercortisolism has emerged as an important consideration [14]. The 2 cases presented here were referred to our center by endocrinologists for consideration of inferior petrosal sinus sampling (IPSS) for the differential diagnosis of ACTH-dependent hypercortisolism [15, 16]. Despite convincing clinical features and

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Table 1. Endogenous hypercortisolism

Neoplastic	Nonneoplastic
ACTH-secreting neoplasm	**Cushing phenotype**
Pituitary (Cushing disease)	Alcohol induced
Ectopic	Chronic kidney disease stages 4–5
	Neuropsychiatric disorders
	Poorly controlled diabetes mellitus
Adrenal nodular disease	Pregnancy
Adenoma/carcinoma	Glucocorticoid resistance
Bilateral nodular disease	Obstructive sleep apnea
Primary pigmented micronodular	
Macronodular	**Non-Cushing phenotype**
	Starvation equivalent disorders
	Relative energy deficiency in sports
	Eating disorders (anorexia/bulimia)

Table 2. Clinical and laboratory differences: neoplastic vs nonneoplastic hypercortisolism

	Neoplastic	Nonneoplastic
History		
Alcohol ≥2/d	---	+++
Hypertension	+++	+++
Diabetes mellitus (type 2)	++	+/-
Low bone density with fractures	+++	---
Physical examination		
Cushingoid facies	+++	++
Dorsocervical fat	++	+
Cutaneous wasting	+++	+
Myopathy	+++	+
Laboratory results		
CKD 1–3	+	+
CKD 4–5	+	+++
Liver ALT > AST	+++	+
Liver AST > ALT	---	+++
LNSC >5× upper limit of reference interval	+++	+
DST AM cortisol >5 mcg/dL	++	++
24-h urine cortisol >4× upper limit of reference interval	+++	+
Positive dDAVP stimulation	+++	---

Abbreviations: CKD, chronic kidney disease; dDAVP, desmopressin acetate; DST, dexamethasone suppression test; LNSC, late-night salivary cortisol.

laboratory findings of the ACTH-dependent Cushing syndrome, both patients had nonneoplastic hypercortisolism. These consultations are intended to emphasize how a good history and examination, simple routine laboratory studies, and more specific diagnostic tests are needed to distinguish neoplastic from nonneoplastic hypercortisolism.

Case 1

A 49-year-old man was referred for IPSS for the differential diagnosis of ACTH-dependent hypercortisolism. He had originally been referred to an endocrinologist because of low testosterone associated with decreased libido. Transdermal testosterone was initiated. He had experienced a 15-kg weight gain in a truncal distribution over the past 4 years with the presence of wide violaceous abdominal striae. He complained of lower extremity edema. He had a 6-year history of type 2 diabetes mellitus treated with metformin and was receiving bumetanide, metolazone, spironolactone, and potassium for hypertension and edema. He was a former cigarette smoker and admitted to 5 to 7 alcoholic drinks weekly.

His blood pressure was 118/70 mm Hg; pulse 88 beats/min; weight 152 kg; body mass index 42 kg/m^2. He was Cushingoid with facial rounding, plethora, and markedly increased supraclavicular fullness. There was no cutaneous wasting. His thyroid, pulmonary, and cardiovascular examinations were normal. His abdomen was grossly distended with fat with wide violaceous striae present. He had normal muscle strength, and slight pretibial edema was present.

Laboratory and imaging results

Laboratory investigation demonstrated mild hypokalemia with chronic kidney disease stage 3, slightly elevated hemoglobin A1C, and elevated liver function tests (Table 3). Basal morning cortisol and ACTH were in the high-normal reference range. Late-night salivary cortisol (LNSC) was elevated on 2 consecutive nights and the overnight 1-mg dexamethasone suppression test (DST) was very abnormal. The 24-hour urine cortisol was in the normal range. Pituitary magnetic resonance imaging scans showed no focal abnormalities.

Case 2

A 54-year-old Black woman was referred for differential diagnosis of ACTH-dependent hypercortisolism with IPSS. She had stage 5 chronic kidney disease and had been on hemodialysis 3 times weekly for the past 7 years. Over the past 2 years, she had a 5-kg weight gain and her hypertension worsened requiring 4 antihypertensive medications (clonidine, furosemide, hydralazine, metoprolol). She had a history of prediabetes; her glycemic control had deteriorated in the past 2 years requiring the addition of insulin glargine therapy. She had a history of obstructive sleep apnea (OSA) treated with continuous positive airway pressure (CPAP) over the past 5 years. She had a low bone density (T-score of femoral neck −2.0 SDs), but no history of fractures. She denied use of alcohol and was a nonsmoker.

Her blood pressure was 155/95 mm Hg, pulse 84 beats/min, body weight 69.1 kg, and body mass index 28.9 kg/m^2. She had facial rounding and an increased accumulation of supraclavicular and dorsocervical fat. She had slight cutaneous wasting with skin-fold thickness of <2 mm in the dorsum of the hand. There was no facial hirsutism. The remainder of her exam was normal.

Laboratory and imaging results

The patient had evidence of chronic kidney disease (CKD)5 with anemia and normal electrolyte composition the day after dialysis (Table 3). She had a slightly elevated hemoglobin

Table 3. Laboratory findings for cases

	Case 1	Case 2	Reference interval
Serum sodium (mEq/L)	139	138	136–145
Serum potassium (mEq/L)	3.4	5.1	3.4–5.1
Serum chloride (mEq/L)	98	99	96–105
Serum bicarbonate (mEq/L)	33	20	22–29
Blood urea nitrogen (mg/dL)	41	65	6–23
Serum creatinine (mg/dL)	1.9	8.9	0.6–1.3
Estimated glomerular filtration rate (mL/min/1.73 cm^2)	39	<10	>60
Hemoglobin A1C (%)	6.7	6.8	<6.5
Alkaline phosphatase (U/L)	138	109	38–129
Aspartate aminotransferase (U/L)	70	27	9–40
Alanine aminotransferase (U/L)	55	31	12–64
Serum cortisol AM (µg/dL)	16.8	18.8	4.8–19.5
Plasma ACTH AM (pg/mL)	35	77	7–63
Serum DHEAS (µg/dL)	30	19	44–331/35–256
LNSC (nmol/L)	11.9, 9.3	4.8, 7.3	<3.2
Urine free cortisol (µg/24 hours)	15	ND	<45
C-reactive protein (mg/dL)	ND	2.3	<0.5
Overnight DST			
Serum cortisol (µg/dL)	8.5	5.1	<1.8
Serum dexamethasone (ng/dL)	233	149	140–295
Plasma ACTH (pg/mL)	19	15	<10

Postdexamethasone ACTH cut-off of <10 pg/mL is from our clinical experience. DHEAS reference ranges are appropriate for sex/age of each case, respectively. Twenty-four-hour urine cortisol not done in Case 2 because of chronic kidney disease.
LNSC, late-night salivary cortisol sampled on 2 separate nights; ND, not done.

A1C, normal liver function tests, and an elevated C-reactive protein. Basal levels of ACTH and cortisol were elevated, and the overnight 1-mg DST demonstrated nonsuppression of ACTH and cortisol with an appropriate dexamethasone level. LNSC on 2 consecutive evenings were elevated. Pituitary magnetic resonance imaging scans showed a subtle 2-mm hypoenhancement in the left pituitary.

Discussion of Cases

Screening for neoplastic hypercortisolism is recommended in patients with physical features of the Cushing syndrome [12]. Endogenous ACTH-dependent hypercortisolism had been firmly established in these 2 cases before referral to our center for IPSS. Both had truncal obesity with progressive weight gain over a few years and they have excessive amount of supraclavicular and dorsocervical fat accumulation. Although this kind of fat redistribution is not specific for hypercortisolism, it does increase the odds ratio for neoplastic hypercortisolism [17]. Cutaneous wasting (skin-fold thickness in the dorsum of the hand <2 mm as seen in case 2) is not a sensitive finding but may be an overlooked physical finding reflecting the catabolic effects of hypercortisolism [18]; however, cutaneous wasting is age dependent, so it lacks specificity in older adults. Neither of our patients had prominent muscle atrophy or proximal myopathy, a finding that typically increases the odds ratio for neoplastic hypercortisolism [17]. Case 1 had a very Cushingoid appearance with facial rounding and plethora.

Recognition of the clinical features of Cushing syndrome may be more challenging in Black patients (case 2), thereby leading to its underappreciation [19]. The presence of wide, violaceous striae was a prominent reason for screening in case 1; this classic finding is uncommon in Cushing syndrome patients older than age 40 years [20, 21] and is rarely observed in patients with mild hypercortisolism. In addition, wide violaceous striae may accompany rapid weight gain (regardless of the cause) in young patients and, therefore, lacks specificity.

Screening for endogenous hypercortisolism in patients with the metabolic syndrome, osteoporosis, and adrenal nodular disease is now accepted by many experienced endocrinologists even in the absence of overt physical findings [17, 22-27]. Our 2 patients had many metabolic derangements that warranted consideration of Cushing syndrome. Both patients had diabetes mellitus and hypertension. A recent multicenter screening study of patients with at least 2 of the following problems (obesity, diabetes with suboptimal glycemic control, hypertension requiring 3 or more antihypertensive medications, or polycystic ovary syndrome) found a prevalence of Cushing syndrome of 7.4% [17]. The presence of low bone density with fractures increases the odds ratio for neoplastic hypercortisolism (case 2 had CKD and low bone density), but metabolic bone disease is common in CKD and is multifactorial. Because low bone density has not been well characterized in patients with nonneoplastic hypercortisolism, the presence of osteoporosis with fracture increases the likelihood of the diagnosis of neoplastic hypercortisolism [28].

Laboratory studies showed elevations of LNSC and abnormal low-dose DSTs in each patient. Of course, urine cortisol was not possible because of anuria in case 2, and it was normal in case 1 possibly from his decreased estimated glomerular filtration rate leading to decreased renal cortisol excretion. Regardless, assessment of urine free cortisol is not a sensitive test for establishing hypercortisolism even in patients with normal renal function. Furthermore, it has been suggested that assessment of urine free cortisol is also not useful as an initial screening test [29]. Nonetheless, both of our patients had biochemical findings consistent with Cushing syndrome with elevations of LNSC and abnormal DST. Case 2 had a possible small pituitary microadenoma that was deceptive because pituitary imaging abnormalities are observed in as many as 20% to 30% of normal subjects and patients with ectopic ACTH-dependent Cushing syndrome [30].

The clues that the hypercortisolism in our patients were due to a nonneoplastic cause were found in their histories and some routine laboratory studies. Case 2 had end-stage kidney failure and had been on hemodialysis for several years. Although not well appreciated, hypercortisolism is common in patients with CKD5 and even milder CKD, and establishing the diagnosis of neoplastic hypercortisolism may be challenging [31]. Case 1 provided a history of 5 to 7 alcohol drinks weekly. Review of his routine laboratory studies over the past 3 years had consistently shown elevated liver function studies with the AST always greater than the ALT. A blood phosphatidylethanol (PEth) level was 420 ng/mL, with >200 ng/mL indicating excessive alcohol intake [32]. After he was confronted with these findings, he admitted that he had been drinking 5 to 7 alcohol drinks daily and that he

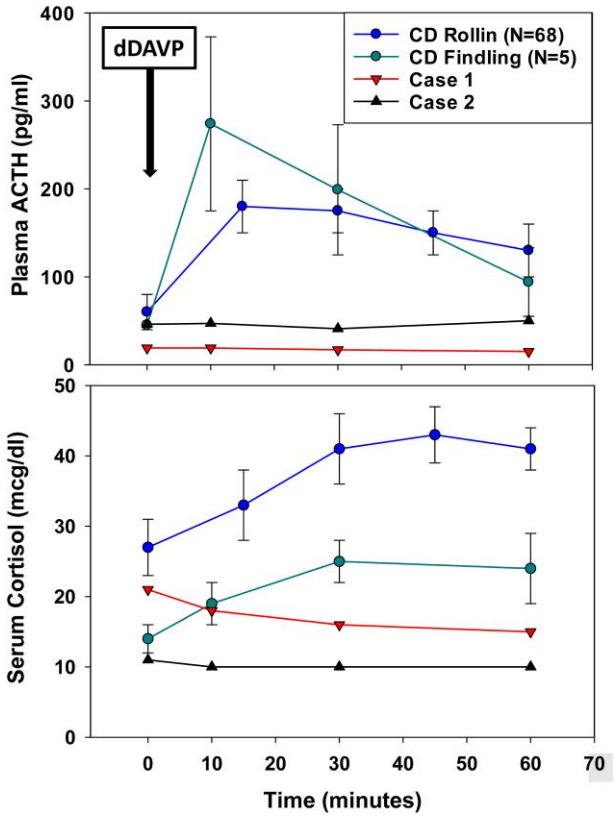

Figure 1. Acute plasma ACTH and serum cortisol response to IV desmopressin (dDAVP) in our 2 cases, a sample of our patients with proven Cushing disease (CD Findling) and adapted from previously published data (CD Rollin) [33].

had been drinking twice that amount 2 years earlier. Alcohol abuse is an established cause of nonneoplastic hypercortisolism and may be overlooked because patients often underreport or hide their alcohol use disorder. Both patients had an absent plasma ACTH and serum cortisol response to desmopressin acetate supporting a diagnosis of nonneoplastic hypercortisolism (Fig. 1). Case 1 entered rehabilitation for his alcohol use disorder and repeat LNSC was normal 3 months later. Case 2 has not had any new clinical findings and continues 3 times weekly hemodialysis.

Nonneoplastic States of Hypercortisolism With Cushing Phenotype (Table 1)

Alcohol-induced hypercortisolism

Initially described in the late 1970s, alcohol-induced Cushing syndrome is among the first disorders reported to cause nonneoplastic hypercortisolism (previously called "alcohol-induced pseudo-Cushing syndrome" [14]). Chronic alcohol use disorder may cause clinical and biochemical features of Cushing syndrome that are indistinguishable from neoplastic hypercortisolism, but that resolve promptly after abstention from alcohol. Despite this well-appreciated phenomenon and the recent increase in alcohol consumption in the United States [34], there have been very few recent reports of alcohol-induced hypercortisolism (AIH).

Patients with AIH may have physical and clinical features and abnormal laboratory findings similar to neoplastic hypercortisolism. (For images of patients with AIH, see [35, 36]). Many studies have confirmed increased cortisol secretion during heavy alcohol use detected with hair cortisol [37], cortisol awakening response [38], overnight urinary cortisol [39], and plasma [40] and LNSC [41]. Animal studies indicate that the mechanism of AIH in increasing HPA axis activity is centrally mediated by hypothalamic CRH and vasopressin [42-44]

Altered peripheral metabolism of cortisol in the liver may be another contributing factor. A patient with AIH was reported to have low plasma ACTH and a prolonged half-life for cortisol [45]. Another potential mechanism is the induction of 11-beta-hydroxysteroid dehydrogenase type 1 gene expression and activity in patients with alcohol liver disease [46]. Therefore, an increase in hepatic cortisol production in patients with alcohol liver disease may contribute to AIH. Nonetheless, if glucocorticoid negative feedback remained intact, normal cortisol levels might be expected unless stimulatory input to the hypothalamus remained intact.

Because the biochemical and clinical features of AIH overlap with true neoplastic Cushing syndrome, clinicians need to be aware of some clues: if patients with hypercortisolism acknowledge more than 1 or 2 alcohol drinks daily or if they have elevations of liver function with the AST > ALT, further investigation is warranted. Blood PEth levels are quite helpful to help quantify the amount of alcohol consumed [47]. Blood PEth analysis measures a group of phospholipids formed in the presence of ethanol and is a biomarker of alcohol intake. Incorporated into phospholipid membrane of red blood cells, PEth has a half-life of 4 to 10 days in blood with a 2- to 4-week window of detection that is prolonged in individuals who chronically or excessively consume alcohol [48]. Many patients with AIH have elevations of AST > ALT, which is common finding in patients with more advanced alcohol liver disease [49]. To provide more certainty of nonneoplastic hypercortisolism in our patients, a desmopressin acetate (dDAVP) stimulation test was performed (see Fig. 1). The lack of a response to dDAVP in the 2 cases we described here are consistent with prior reports [50] and confirmed nonneoplastic, ACTH-dependent hypercortisolism [51].

Chronic kidney disease

Many of the signs and symptoms of neoplastic endogenous hypercortisolism are evident in patients with renal failure, suggesting a common mechanism: activation of the glucocorticoid receptor [31]. Renal excretion of cortisol conjugated in the liver is the primary route of clearance of circulating cortisol [52-56]. Therefore, one might hypothesize that serum cortisol might be increased in patients with poor renal function from a decreased steroid clearance rate or perhaps changes in plasma corticosteroid binding globulin [57]. However, if the feedback mechanisms of the HPA axis controlling circulating serum free cortisol are operating normally [10, 11], the system should be able to restore circulating cortisol to normal even in the face of decreased metabolic clearance rate. This is not the case because mild hypercortisolism is a common finding in patients with renal failure [31, 57-62], and it is possible for patients with neoplastic hypercortisolism to have renal failure, complicating the diagnosis [63]. The hypercortisolism and associated glucocorticoid-mediated features of renal failure are centrally, ACTH driven and likely from a decreased sensitivity to glucocorticoid negative feedback and a reduction in the activity of 11-beta-hydroxysteroid dehydrogenase type 2 in the kidney [61, 62, 64, 65].

We and another group have demonstrated that patients with CKD on hemodialysis have a normal morning peak in cortisol but a failure to achieve the circadian nadir on nondialysis days in a similar pattern to mild neoplastic hypercortisolism [62, 66, 67]. This is clearly driven by central mechanisms (ie, ACTH) likely from the cumulative stress of the CKD, increased inflammatory state, and every-other-day hemodialysis [62]. Even milder CKD (stages 3 and 4) results in a similarly altered circadian rhythms [57, 58, 68]. It is important to emphasize that most patients with severe CKD have an abnormal low-dose DST [61]. Again, this appears to be centrally driven because the failure to suppress cortisol after a 1-mg DST correlated with the degree of CKD, although it is possible that changes in cortisol clearance could compound the problem [57].

Regardless of the mechanism of hypercortisolism, a normal late-night salivary cortisol is useful to rule out suspected neoplastic hypercortisolism in patients with renal failure [57, 58, 62]. If late-night salivary cortisol is moderately increased and the patient clearly has ACTH-dependent hypercortisolism, we suggest consulting an endocrinologist with extensive experience in the evaluation of HPA axis disorders. In our experience, patients with nonneoplastic hypercortisolism associated with CKD fail to exhibit an ACTH response to dDAVP.

Neuropsychiatric disorders

Neuropsychiatric disorders can result in a centrally mediated chronic increase in HPA axis activity [14]. These include major depression, anxiety/panic disorders, obsessive/compulsive disorder, schizophrenia, and autism spectrum disorder [69, 70]. A meta-analysis of the "stress response" in these patients found variable results that appear to be sexually dimorphic [71]. The consensus is that the desmopressin stimulation test is appropriate to distinguish between neoplastic, ACTH-dependent Cushing syndrome and endogenous depression [72-74], but that the combined CRH-desmopressin test is not useful [75]. Finally, there are many stress-related psychiatric disorders that are not associated with increases in HPA axis activity, illustrating that it is important to consider each syndrome individually and with clarity, specificity, and precision [76].

Poorly controlled type 2 diabetes mellitus

Cortisol is the archetypal glucocorticoid because of its stimulation of hepatic gluconeogenesis and induction of insulin resistance. Therefore, it is a reasonable conjecture that cortisol could mediate the development of type 2 diabetes mellitus [77]. There are varied opinions about whether patients with poorly controlled diabetes mellitus have chronic activation of the HPA axis (reviewed in [77, 78]) possibly because of its "subclinical" nature [9]. The use of the desmopressin test may be useful in patients with type 2 diabetes mellitus in whom non-neoplastic Cushing syndrome is suspected [79]. There has been an interesting proposal that, if indeed the HPA axis is dysregulated in type 2 diabetes mellitus, that stress and depression may be important mediators and/or covariates in the development of insulin resistance [80].

Glucocorticoid resistance

This is a familial receptor-mediated disorder with otherwise unexplained increase in cortisol production [81]. It is now accepted that it is caused by genetic defects in the *NR3C1* gene that encodes for the glucocorticoid receptor protein [82]. Furthermore, common cellular mechanisms identified include activation of the mitogen-activated protein kinases and/or alterations in expression of the dual-specific phosphatases [83]. The lack of features of glucocorticoid excess with the features of androgen excess are because the peripheral tissues are relatively insensitive to cortisol but maintain sensitivity to androgens and mineralocorticoids. Because the cortisol resistance is not complete, patients typically compensate with increases in plasma ACTH and cortisol [84]. Findings can include chronic fatigue and hypertension with or without hypokalemic alkalosis, hyperandrogenism, or the catabolic features of hypercortisolism. Nonetheless, excessive adrenal mineralocorticoid secretion, hypokalemia, and hypertension with hypercortisolemia may be confused with neoplastic hypercortisolism. In women, hyperandrogenism can result in hirsutism, menstrual irregularities, and oligomenorrhea with decreased fertility. In men, glucocorticoid resistance may lead to infertility and, in children, to precocious puberty [85]. Both autosomal dominant and recessive inheritance have been described [86]. Finally, although extremely rare, there are reports of glucocorticoid receptor hypersensitivity in patients with low serum cortisol in whom the features of hypercortisolism appear when the patients receive exogenous glucocorticoids [87].

Pregnancy

Serum-free and salivary cortisol increase during pregnancy [88, 89]. Furthermore, serum corticosteroid-binding globulin increases during pregnancy because of a hepatic effect of estrogen [90]. As in other nonneoplastic causes of hypercortisolism, one would expect negative feedback control to prevent the increase in free (bioactive) plasma cortisol. Therefore, the increase in serum-free and salivary cortisol is driven by the increase in plasma ACTH [91]. Several mechanisms have been proposed for the increase in plasma ACTH, including the secretion of CRH from the placenta, the increase in progesterone that can act as a glucocorticoid antagonist, a decrease in glucocorticoid negative feedback sensitivity, and production of ACTH from the placenta [14, 92]. It seems that both environmental and biological factors contribute to the activation of the HPA axis during pregnancy [93]. It is likely that the increase in bioactive (free) cortisol is of metabolic benefit during pregnancy.

Obstructive sleep apnea

OSA, a disorder often associated with obesity, increases the activity of the HPA axis, and consistent use of CPAP seems to attenuate this effect [94]. However, when examined using salivary cortisol sampling to minimize environmental stress, frequent hypoxic/apneic episodes do not increase diurnal cortisol levels, but anticipation of the application of CPAP seems to be an acute stressor [95]. Furthermore, withdrawal of CPAP with recurrence of severe OSA does not increase HPA axis activity, suggesting habituation to the multiple stressors and comorbidities associated with OSA [96]. Adding to the confusion is that OSA interacts with typical features of increased cortisol (obesity and insulin resistance/type 2 diabetes mellitus as in our case 2) to bring on nonneoplastic hypercortisolism, and, in that scenario, CPAP does normalize this effect [97]. Therefore, although OSA has the potential to chronically activate the HPA axis in humans, the comorbidities associated with OSA are critical confounding covariates to consider.

Nonneoplastic States of Hypercortisolism Without the Cushing Phenotype: Starvation Equivalent Disorders

Although typically not a diagnostic dilemma, there are other nonneoplastic causes of chronically increased HPA axis activity.

Relative energy deficiency in sport

One of these situations is intense chronic exercise exceeding caloric intake [98, 99]. This is now termed the "relative energy deficiency in sport" and is receiving increased international scrutiny [100, 101]. One of the more interesting studies on this was in elite athletes in a variety of fields (road-cycling, long- and middle-distance running, triathlon, race-walking, rowing, wrestling, biathlon, Nordic combined, cross-country skiing, boxing, powerlifting, soccer, or handball) [102]. They found a prevalence of subclinical hypercortisolism of 23% in their subjects, several of whom had an association with other markers of relative energy deficiency in sport. The same group found an increase in cortisol during a 4-week intensified endurance training intervention in well-trained male cyclists that, like many studies of exercise in human subjects, illustrates the multiple confounders that one must consider in this scenario [103]. For example, exercise training does not alter the HPA response to a psychological stressor [104], so drawing general conclusions about exercise and acute and chronic HPA axis dynamics is challenging.

Eating disorders

Starvation associated with anorexia nervosa both acutely and chronically increases the activity of the HPA axis leading to hypercortisolism [105-111]. This has been demonstrated by increases in 24-hour urine free cortisol, increased LNSC, and abnormal overnight DSTs (reviewed in [108]). Of relevance to the current article is, like in other states of nonneoplastic hypercortisolism, there is failure of desmopressin to stimulate ACTH release in anorexia nervosa [110, 112]. Several mechanisms for hypercortisolism have been proposed including chronically increased, glucocorticoid insensitive hypothalamic CRH release and/or an alteration in negative feedback sensitivity at the level of the hippocampus [108, 113]. Of interest is the finding that, whereas basal cortisol levels are increased with anorexia nervosa, the response to an acute psychological stressor is attenuated also, possibly because of increase ambient cortisol negative feedback [114]. It is clear that depression and anxiety are comorbid events associated with starvation in patients with anorexia nervosa like other complex syndromes of nonneoplastic hypercortisolism [115].

It is fascinating to note that, although weight recovery can ameliorate some of the pathophysiological findings in anorexia nervosa [116], it does not appear to normalize the hypercortisolism; this leads to the radical hypothesis that the increase in HPA axis activity has a neurological basis parallel to, but not caused by, whole-body deficiency in energy stores in anorexia nervosa [108, 114, 115, 117]. In fact, it may be that cortisol mediates some of the psychopathology in patients with anorexia nervosa rather than merely responding to the energy deficiency [108, 116, 117]. Supporting this notion is the finding that constitutional "thinness" has very different HPA axis behavior than patients with true anorexia nervosa [118]. This highlights the concept that the neurologic (probably hypothalamic) set-point for body mass is an important controller of the HPA axis, and that deviation from this set-point is a major factor leading to hypercortisolism [119]. Despite the potentially negative effects of hypercortisolism in anorexia nervosa, therapy directed at the HPA axis is not recommended because this pathophysiological response may be important for survival [108].

Studies to Differentiate Neoplastic and Nonneoplastic Hypercortisolism (Table 2)

Initial laboratory evaluation

The 3 accepted complementary screening tests for the evaluation of endogenous hypercortisolism are LNSC; assessment of the circadian nadir), 24-hour urine cortisol (index of 24 hour cortisol secretion), and the low-dose DST (assessment of glucocorticoid negative feedback sensitivity) [10, 120]. Each has advantages and disadvantages [12]. Significant elevation of LNSC (>5× upper limit of normal) and urine cortisol (>4× upper limit of normal) usually supports the diagnosis of neoplastic hypercortisolism, but the postdexamethasone cortisol level is less helpful (Table 2). Equivocal or discordant results from these studies may cause confusion for the clinician and angst for the patient. In this circumstance, the best approach is to provide reassurance, repeat the studies if there is a sufficient index of suspicion, and monitor the patient for clinical progression of signs and symptoms. Also, be prepared for patients who raise the possibility of intermittent or cyclical hypercortisolism [121]. To aggravate the situation, the patient may have a vague and sometimes ephemeral pituitary imaging abnormality or an incidentally discovered adrenal nodule (which may have led to the initial diagnostic studies) that only amplifies the apprehension. More specific diagnostic testing with dDAVP may be necessary to provide clarity.

Imaging

Neither pituitary nor adrenal imaging studies should be used alone to confirm the presence or absence of neoplastic hypercortisolism. As case 2 demonstrated, small pituitary imaging abnormalities occur in many normal subjects and as many as 30% of patients with ectopic ACTH [30]. In addition, IPSS will not be useful because normal subjects and patients with Cushing disease will have a pituitary ACTH gradient [122]. Clinicians should also not be seduced by the radiological finding of adrenal nodules or enlargement. Patients with ACTH-dependent hypercortisolism may harbor an adrenal nodule [123], and adrenal nodules have been reported in patients with AIH [124]. In addition, bilateral adrenal enlargement may occur in as many as 50% of depressed patients [125, 126].

Desmopressin acetate stimulation test

With the current lack of availability of CRH for injection for diagnostic purposes, the use of dDAVP stimulation to examine HPA axis function has gained interest [51, 127, 128] (Table 4). Vasopressin acts through 3 distinct receptors [130-132]: V1 (or V1a) receptors mediate the pressor effects of vasopressin and hepatic effects on glycogenolysis and neoglycogenesis; V2 receptors are responsible for the antidiuretic effects and hemostatic effects of vasopressin; and V3 (or V1b) receptors are in the pituitary and help vasopressin stimulate ACTH secretion.

Table 4. Morning desmopressin acetate stimulation test protocol

- Study should begin before 9:00 AM
- Indwelling IV catheter inserted, then wait 10 minutes before the first blood draw
- Measurements at each study timepoint:
  - Plasma ACTH and serum cortisol
  - Blood pressure and pulse rate
- After baseline blood draw, infuse desmopressin acetate)[a] 10 mcg (2.5 mL) IV over 60 seconds followed by a 2-mL saline flush
- Draw blood samples for plasma ACTH and cortisol at −15 minutes, 0 minutes (baseline), +10, +20, +30, +45, and +60 minutes
- Interpretation: positive response:
  - Increase in plasma ACTH above baseline >30 pg/mL[b] or peak ACTH >70 pg/mL
  - Increase in serum cortisol[c] >6 mcg/dL or peak >18 mcg/dL

[a]Side effects may include flushing, increased respiratory rate, hypotension (rare); if hypotension occurs immediately notify physician. Hypotension may result in a false positive test. Patients should restrict fluid intake to 40 ounces (1.2 L) for the next 24 hours.
[b]Percentage increase over baseline is used by some (ranging from 35% to 150%)
[c]Percentage increase over baseline is used by some (ranging from 20% to 40%). Cortisol cutoffs depend on the assay method used [129].

Desmopressin is a vasopressin analog that is relatively specific for the V2 receptor and has relatively weak affinity for V3 (V1b) receptors. Corticotroph adenomas often have an aberrant expression of V3 (V1b) receptors, although there is controversy concerning the expression of the tumoral vasopressin receptor subtypes [133-137]. Consequently, many patients with ACTH-secreting pituitary adenomas will have an exaggerated ACTH and cortisol response to dDAVP administration [138, 139]. In contrast, healthy subjects and patients without ACTH-secreting tumors usually have an absent or minimal ACTH and cortisol response to dDAVP [139]. dDAVP is now used as a substitute for CRH to stimulate ACTH secretion during IPSS for the differential diagnosis of ACTH-dependent neoplastic hypercortisolism [140-143]. An exaggerated ACTH response to dDAVP is also an early predictor of recurrence of Cushing disease [51, 144-149]. The most important use of this test may be the help it provides in distinguishing patients with ACTH-driven neoplastic hypercortisolism from patients with nonneoplastic hypercortisolism. Because a small number of patients with nonpituitary (ectopic) ACTH secreting have a robust ACTH response to dDAVP, it should not be used for the differential diagnosis of ACTH-dependent neoplastic hypercortisolism [150].

The time of day the dDAVP test is performed may also be quite important. Scott et al showed that 11 of 18 normal subjects were "responders" to IV dDAVP when the test was performed in the afternoon [151]. Accordingly, we recommend that the dDAVP stimulation test be performed in the morning (before 9 AM).

The negative dDAVP test in our 2 cases helped us exclude neoplastic ACTH-dependent hypercortisolism (Fig. 1). In contrast, the outmoded dexamethasone-CRH test is typically abnormal in AIH and similar to patients with Cushing disease [152]. The dDAVP test has also shown reasonably good sensitivity and specificity for identifying nonneoplastic hypercortisolism in states of obesity, neuropsychiatric disorder, and polycystic ovary syndrome from patients with neoplastic hypercortisolism [139]. To our knowledge, the ACTH response to dDAVP has not been studied to evaluate the HPA axis in patients with CKD.

Performing the dDAVP test is simple and can be accomplished in most endocrine diagnostic settings (Table 4). There are 2 important points about this test: (1) as stated previously, the test should be performed in the morning and (2) fluid restriction (eg, <1.2 L) for 24 hours after test is essential. Some subjects may notice a decrease in urine output and, unfortunately, increase their fluid intake, possibly leading to hyponatremia.

Interpretation of the dDAVP test is a work in progress; what constitutes a positive response that reliably distinguishes neoplastic hypercortisolism from nonneoplastic hypercortisolism varies in the literature [51]. Unfortunately, there is a lack of studies in otherwise healthy, obese subjects to frame an abnormal response. The peripheral ACTH response to dDAVP in patients with Cushing disease is rapid with an increase within 5 to 10 minutes [33] (see Fig. 1). Another potential confounding factor is the lack of harmonization of ACTH assays. Furthermore, the commonly used Siemens Immulite ACTH assay may be unreliable and unpredictable [153-155] and should be avoided in general despite the convincing results of Rollin et al [[33] see Fig. 1]. It is our experience that an ACTH Δ response >30 pg/mL or a peak response >70 pg/mL provides the best criteria for the diagnosis of Cushing disease. The cortisol response to dDAVP is less discriminatory (see Fig. 1) and a positive response has been reported anywhere from a Δ of 4 to 8 mcg/dL or a peak response of >18 mcg/dL. A percent change in ACTH and/or cortisol (eg, a change in ACTH of >50%) after dDAVP has also been proposed (Table 4) [33]. This is counterintuitive because a small increase in ACTH (eg, from 20 to 31 pg/mL [a 52% increase]), might be considered positive for Cushing disease using the percent increase approach.

The dexamethasone suppression and desmopressin stimulation tests have been combined to theoretically improve diagnostic performance [139, 156, 157]. Of course, dexamethasone suppresses the normal corticotrophs and any observed response to dDAVP should be due to tumorous corticotrophs. A greater than 50% increase in cortisol and ACTH after combined dexamethasone desmopressin test has a 100% sensitivity and 89% specificity for predicting recurrence of Cushing disease [158]. To our knowledge, this approach has not been adequately studied to differentiate neoplastic and nonneoplastic hypercortisolism; this is certainly worthy of investigation. In summary, the results of dDAVP testing needs to be interpreted in the context of a thorough clinical evaluation and consideration of the patient's history, physical examination, routine laboratory studies, modern biochemical studies of HPA function, and the pretest probability of true Cushing syndrome.

Summary and Research Opportunities

The diagnosis and differential diagnosis of the disorder initially described by Harvey Cushing is acknowledged as the most challenging in endocrinology (Table 5). There are many patients with clinical features of this syndrome who do not have biochemical evidence of hypercortisolism and do not warrant further investigation. The awareness that mild cortisol excess (even in the absence of the clinical syndrome) in patients with adrenal nodular disease may be associated with increased risk for cardiometabolic morbidity and mortality as well as metabolic bone disease has increased screening for

Table 5. Summary of major points

- Clinical findings of hypercortisolism from nonneoplastic causes (formerly known as pseudo-Cushing syndrome) are often clinically and biochemically indistinguishable from neoplastic causes (particularly ACTH-dependent Cushing syndrome).
- There are many causes of nonneoplastic hypercortisolism, of which alcohol use disorder and renal failure are common.
- Alcohol-induced hypercortisolism may be suspected in patients with elevated liver function tests if the AST > ALT; blood phosphatidylethanol will help identify a patient with an alcohol use disorder.
- The lack of an acute ACTH and cortisol response to desmopressin acetate is a reliable approach to confirm the clinical suspicion of nonneoplastic hypercortisolism

hypercortisolism. However, the HPA axis is dynamic and provoked by many chemical (alcohol), inflammatory (CKD), psychologic (chronic stress and major depression), and physical (chronic intense exercise/starvation) stimuli. It is not surprising that these chronic, protracted or intermittent, stimuli may cause endogenous hypercortisolism resulting in physical features of excessive glucocorticoid exposure.

Our 2 cases illustrate this conundrum. Both patients had striking clinical features and were suspected to have neoplastic hypercortisolism. They highlight the importance of a thorough history and examination complemented by the appropriate laboratory studies. Case 1 provided a history of almost daily alcohol consumption (albeit underestimated) and had liver function test elevations (AST > ALT) that raised the likelihood of an alcohol use disorder that can cause endogenous, centrally mediated hypercortisolism. Case 2 had CKD5, which is often associated with nonneoplastic hypercortisolism.

The laboratory findings in our patients were also indistinguishable from neoplastic hypercortisolism. A secure laboratory confirmation of true Cushing syndrome may be further compromised by surreptitious use of corticosteroids, use of pharmacologic agents that affect the diagnostic testing (eg, oral contraceptives that alter serum corticosteroid-binding globulin levels and drugs that alter dexamethasone clearance), improper test execution and problematic hormone assays, and incidentally discovered, nonspecific pituitary and adrenal imaging abnormalities. Although we recommend the dDAVP stimulation test to aid in the confirmation of neoplastic hypercortisolism, we realize that this test needs more extensive investigation with better standardization of reference intervals using reliable and harmonized ACTH and cortisol assays in diverse patient populations. In fact, a recent comprehensive review of the dDAVP test in the diagnosis of Cushing syndrome did not specifically call out either alcohol-induced hypercortisolism or CKD as common causes of nonneoplastic hypercortisolism for which the test might be useful [51]. Using a percentage change in ACTH and cortisol as diagnostic criteria seems hazardous and too analogous to the misguided use of percentage change in cortisol after ACTH (cosyntropin) stimulation for the diagnosis of adrenal insufficiency. Finally, there will be some hypercortisolemic patients with equivocal clinical, biochemical, and imaging findings in whom a diagnosis of neoplastic hypercortisolism may be uncertain. It is often prudent to wait for several months to assess any progression in clinical features and repeat laboratory investigations; this may provide clarity in the diagnosis. Referral to a center with more experience in the diagnosis and differential diagnosis of Cushing syndrome for another opinion is always a good option.

More high-quality clinical studies are needed to understand the frequency, magnitude, and impact of HPA axis hyperactivity on the dysmetabolic findings in AIH, CKD, and poorly controlled diabetes. It is possible that pharmacotherapy directed at these states of nonneoplastic hypercortisolism may improve the metabolic derangements and the quality of life. We anticipate that there will be increasing awareness of other disorders such as chronic pain states and congestive heart failure in which mitigating the effects of hypercortisolism may be a useful therapeutic approach [159-161].

Disclosures

J.W.F. is a consultant for Corcept Therapeutics and Recordati. H.R. is a consultant and receives research reagents from Corcept Therapeutics and is a consultant and does research for Cerium Pharmaceuticals. None of these disclosures represent a conflict of interest for the current publication.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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