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Comparison of the Dexamethasone-Suppressed Corticotropin-Releasing Hormone Test and Low-Dose Dexamethasone Suppression Test in the Diagnosis of Cushing's Syndrome

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Context: The low-dose dexamethasone suppression test (LDDST) is widely used in confirming a diagnosis of Cushing's syndrome. CRH administration at the end of an LDDST has been reported to improve the diagnostic accuracy of this test.

Objective: Our objective was to assess whether CRH administration after a standard LDDST (LDDST-CRH test) improves diagnostic accuracy in Cushing's syndrome.

Design, Setting, and Participants: Thirty-six individuals with a clinical suspicion of Cushing's syndrome each completed a standard LDDST and an LDDST-CRH test at Hammersmith Hospitals NHS Trust, London. The LDDST involved administration of 0.5 mg oral dexamethasone given 6-hourly for 48 h. Serum cortisol was measured 6 h after the last dose of dexamethasone, with a value of 50 nmol/liter or below excluding Cushing's syndrome. Immediately after this, the LDDST-CRH test commenced with administration of a ninth dose of 0.5 mg dexamethasone. Exactly 2 h later, 100 μg human-sequence CRH was administered. Serum cortisol was measured 15 min after the CRH injection, with a value of less than 38 nmol/liter also excluding Cushing's syndrome.

Main Outcome Measure: Diagnosis or exclusion of Cushing's syndrome was the main outcome measure.

Results: Twelve subjects were diagnosed with Cushing's syndrome (eight Cushing's disease and four primary adrenal). The sensitivity of the LDDST in diagnosing Cushing's syndrome was 100%, with a specificity of 88%. In contrast, although the sensitivity of the LDDST-CRH test was also 100%, specificity was reduced at 67%. These results give a positive predictive value of 80% for the LDDST and 60% for the LDDST-CRH test.

Conclusion: This small study suggests that the addition of CRH to the LDDST does not improve the diagnostic accuracy of the standard LDDST in Cushing's syndrome. **(*J Clin Endocrinol Metab* 91: 2582–2586, 2006)**

DIFFERENTIATING BETWEEN CUSHING'S syndrome and pseudo-Cushing's states in individuals with hypercortisolism is difficult because of the increasing prevalence of obesity, hypertension, and type II diabetes mellitus (1–4). Liddle's original description of the low-dose dexamethasone suppression test (LDDST) (5) has been refined in recent years to measure serum cortisol by RIA. Current practice involves the standard LDDST whereby 0.5 mg dexamethasone is administered orally at strict 6-hourly intervals for 48 h, with a cutoff value for suppression of serum cortisol to 50 nmol/liter or below being 98% sensitive for the diagnosis of Cushing's syndrome (6). However, some individuals with Cushing's syndrome may also adequately suppress their serum cortisol to less than 50 nmol/liter during a standard LDDST (7), which may reflect impaired dexamethasone clearance (8, 9).

Yanovski *et al.* (10) proposed that CRH administered immediately after low-dose dexamethasone administration (dexamethasone-suppressed CRH stimulation test), was superior to the standard LDDST in the diagnosis of Cushing's syndrome. Current opinion suggests that in pseudo-Cushing's syndrome, CRH secretion is increased, yet cortisol continues to exert negative feedback on the remainder of the hypothalamic-pituitary-adrenal axis, hence allowing suppression by exogenous glucocorticoid. In contrast, in individuals with Cushing's syndrome, the hypothalamic-pituitary-adrenal axis is more responsive to exogenous CRH but less responsive to suppression by dexamethasone. Using the dexamethasone-suppressed CRH stimulation test, a serum cortisol of greater than 38 nmol/liter 15 min after CRH administration distinguished Cushing's syndrome from pseudo-Cushing's states with 100% sensitivity and specificity (10). More recently, the same group showed that the dexamethasone-suppressed CRH stimulation test also correctly distinguished all subjects with mild Cushing's disease from healthy volunteers (11).

We evaluated the effects of CRH post-dexamethasone suppression in the diagnosis of Cushing's syndrome. By modifying previously described protocols (10, 11), our subjects underwent a standard LDDST and after completion of this, received CRH (LDDST-CRH test). This enabled us to inves-

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Abbreviations: CS-excluded, Cushing's syndrome excluded; LDDST, low-dose dexamethasone suppression test; LDDST-CRH test, dexamethasone-suppressed CRH test; MRI, magnetic resonance imaging.

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tigate subjects by usual diagnostic criteria yet also to study any additional diagnostic benefits of CRH administration after dexamethasone suppression.

Patients and Methods

Patients

A cohort of 36 individuals who were suspected to have Cushing's syndrome based on the presence of typical clinical characteristics (1) underwent our standard investigative protocol. Each subject completed a standard LDDST and an LDDST-CRH test between 2002 and 2004 at Hammersmith Hospitals NHS Trust, London. No individuals had significant renal or hepatic disease. Subjects were admitted to the Clinical Investigations Unit at Hammersmith Hospital for LDDST-CRH testing and had stopped any estrogen- or glucocorticoid-containing preparations for 6 wk before the test. None were taking medications known to induce liver enzymes such as anticonvulsants at the time of the study. After investigation of these 36 individuals, there were 12 confirmed cases of Cushing's syndrome (eight Cushing's disease and four primary adrenal). Three subjects had a clear underlying cause for pseudo-Cushing's syndrome (alcohol excess in two, morbid obesity and obstructive sleep apnea in one) that was addressed before repeat biochemical testing. Sixteen subjects had Cushing's syndrome excluded on biochemical testing (CS-excluded). The study protocol was approved by our local research ethics committee, and informed consent was obtained. Studies were performed in accordance with the Declaration of Helsinki.

Study protocol

A standard LDDST involved 0.5 mg oral dexamethasone given 6-hourly (0900, 1500, 2100, and 0300 h) for 48 h with a final plasma cortisol sample taken 6 h after the last dose of dexamethasone (7). In contrast, the dexamethasone-suppressed CRH stimulation test (10, 11) starts at 1200 h, again with eight doses of 0.5 mg oral dexamethasone administered 6-hourly (1200, 1800, 2400, and 0600 h). However, a blood sample for serum cortisol is taken 44 h after the start of the test, 2 h after the last dose of dexamethasone (0800 h) and just before administration of iv CRH. A final blood sample is taken 15 min later. We adapted the Yanovski protocol to maintain the final 48-h time point of the standard LDDST so that biochemical diagnosis or exclusion of Cushing's syndrome was not compromised in our subjects. In our protocol (LDDST-CRH test), individuals received 0.5 mg dexamethasone orally every 6 h (0900, 1500, 2100, and 0300 h) for 48 h. Forty-eight hours after the first dexamethasone dose (T = 48 h), a blood sample for serum cortisol was taken, concluding the standard LDDST. Immediately after this, the LDDST-CRH test commenced. A ninth dose of 0.5 mg dexamethasone was given to maintain cortisol suppression before CRH administration, and after this, subjects were advised to remain nil by mouth to minimize alterations in dexamethasone absorption. Exactly 2 h after the ninth dose, a blood sample was taken (T = 50 h) just before an iv bolus injection of 100 μg human-sequence CRH (human corticorelin-trifluorate; Ferring Pharmaceuticals Ltd., Berkshire, UK). A final blood sample was collected exactly 15 min after CRH injection (T = 50 h + 15).

Using the LDDST alone, a serum cortisol of 50 nmol/liter or below excluded Cushing's syndrome (6). Based on the dexamethasone-suppressed CRH stimulation test protocol (10, 11), serum cortisol of less than 38 nmol/liter 15 min after CRH injection (T = 50 h + 15) also excluded Cushing's syndrome. Therefore, in those patients achieving serum cortisol values below both cutoff values, Cushing's syndrome was excluded. Individuals with serum cortisol values exceeding both cutoffs were diagnosed with Cushing's syndrome and underwent additional investigations to identify the cause. Subjects with low or suppressed ACTH underwent a computed tomography scan of the adrenal glands to confirm an adrenal source. All four individuals with adrenal-dependent Cushing's syndrome had low/suppressed ACTH with a solitary adrenal mass on imaging. All those with ACTH-dependent Cushing's syndrome underwent a magnetic resonance imaging (MRI) scan of the pituitary gland and bilateral inferior petrosal sinus sampling to distinguish Cushing's disease from ectopic ACTH production. In those three individuals in which the pituitary MRI did not show a mass lesion, inferior petrosal sinus sampling confirmed and lateralized a pituitary source of ACTH.

The diagnosis of Cushing's syndrome was verified by histological examination of a pathological specimen after surgery. In those cases where histological confirmation was not possible, diagnosis was confirmed if clinical and biochemical remission of Cushing's syndrome occurred after surgery. In all cases of adrenal-dependent Cushing's syndrome, there was remission of symptoms with biochemical confirmation of cure on standard LDDST. Six subjects with Cushing's disease were cured after transsphenoidal hypophysectomy. However, two subjects with Cushing's disease, confirmed by inferior petrosal sinus sampling, did not have histology supporting removal of an ACTH-secreting pituitary adenoma and did not display clinical evidence of cure postoperatively. This was confirmed after MRI and repeat standard LDDST before definitive treatment with bilateral adrenalectomy.

Subjects diagnosed with pseudo-Cushing's syndrome and those subjects in which Cushing's syndrome was excluded (CS-excluded) were followed up for progression of Cushingoid features. These subjects were followed up for at least 1 yr or until we were confident that Cushing's syndrome had been excluded because of lack of progression of clinical symptoms in addition to exclusion on biochemical grounds.

RIA

Plasma cortisol was measured using the Nichols Advantage one-site chemiluminescence cortisol assay (Nichols Institute Diagnostics, San Clemente, CA). The intraassay coefficient of variation was 4.7%. The interassay coefficients of variation were as follows: low values (mean cortisol, 69.6 nmol/liter) 5.5%, medium values (mean cortisol, 452.3 nmol/liter) 4.4%, and high values (mean cortisol, 814.2 nmol/liter) 3.8%. The reported analytical sensitivity of the assay is 22 nmol/liter, and the functional sensitivity is 54 nmol/liter. In our laboratory, the functional sensitivity (defined as the concentration with a coefficient of variation not to exceed 10%), when estimated from a precision profile using Nichols reagents, was no more than 15 nmol/liter (see supplemental Table 1, published as supplemental data on The Endocrine Society's Journals Online web site at http://www.jcem.endojournals.org). There was 1.6% cross-reactivity with 11-deoxycortisol and 5.9% with corticosterone and no significant cross-reactivity with other naturally occurring steroids.

Statistical analysis

Sensitivity and specificity for the standard LDDST and LDDST-CRH were derived from receiver operating characteristic analysis (12) (Stata version 7.0). The diagnostic accuracy of the standard LDDST and LDDST-CRH test was compared using the paired exact test. $P < 0.05$ was considered to be statistically significant.

Results

The results for each subject (no. 1–36) after an LDDST and LDDST-CRH test are shown in Table 1. After a standard LDDST, all 12 subjects with Cushing's syndrome failed to suppress their T = 48 h serum cortisol to less than 50 nmol/liter (Fig. 1), giving a sensitivity of 100%. Three individuals with pseudo-Cushing's syndrome also failed to suppress their T = 48 h serum cortisol to below this level, giving the LDDST a specificity of 88%. In each of these three cases, addressing the cause of the pseudo-Cushing's state (noninvasive ventilation for obstructive sleep apnea associated with morbid obesity for subject 13 and alcohol abstinence for subjects 14 and 15) resulted in adequate suppression of serum cortisol at T = 48 h on repeat LDDST-CRH testing.

After the LDDST-CRH test, the T = 50 h + 15 serum cortisol was greater than 38 nmol/liter in all 12 Cushing's subjects, giving a sensitivity for this test of 100% in the diagnosis of Cushing's syndrome. Because three pseudo-Cushing's subjects and five CS-excluded subjects had a T = 50 h + 15 serum cortisol that was greater than 38 nmol/liter, the specificity of the LDDST-CRH test was 67% (Fig. 2 and

TABLE 1. Values for serum cortisol after completion of a LDDST (T = 48 h) and LDDST-CRH test (T = 50 h + 15) in Cushing's syndrome (CS), pseudo-Cushing's states, and in those in which Cushing's syndrome was excluded (CS-excluded)

Subjects	UFC (nmol/24 h)	Serum cortisol (nmol/liter)	
		LDDST T = 48 h	LDDST-CRH test T = 50 h + 15
CS, pituitary			
1	585	275	909
2	705	79	137
3	123	58	122
4		1715	1620
5	607	54	54
6	459	172	242
7	650	437	797
8	1559	932	610
CS, adrenal			
9	930	514	624
10	506	68	63
11	640	1630	1631
12	333	932	77
Pseudo-Cushing's			
13	340	82	73
14	421	52	41
15	44	55	62
CS-excluded			
16	385	30	28
17		30	31
18	264	28	32
19	532	23	21
20	102	35	25
21	303	50	<22
22	217	30	30
23	28	35	<22
24	253	37	36
25	71	<22	<22
26	120	<22	<22
27		39	19
28	85	<22	<22
29		41	<22
30		34	35
31		32	27
Discordant results			
32	96	45	41
33		39	233
34	290	<22	49
35		45	45
36	237	31	42

Cushing's syndrome was excluded if patients suppressed serum cortisol to 50 nmol/liter or below after an LDDST or to below 38 nmol/liter after an LDDST-CRH test, with no clinical progression of features of Cushing's syndrome. In those subjects with discordant results, serum cortisol was suppressed to 50 nmol/liter or below on completion of an LDDST but elevated above 38 nmol/liter after CRH administration. These individuals were followed up for progression of Cushingoid features until we were confident that Cushing's syndrome had been excluded both clinically and on biochemical grounds. UFC, Mean 24-h urinary free cortisol (normal range, 55–270 nmol/24 h).

Table 1) (see supplemental Table 2 for clinical features of pseudo-Cushing's and CS-excluded subjects).

Five subjects (no. 32–36), demonstrated discordant results comparing the standard LDDST and LDDST-CRH test. Their clinical features are shown in Table 2. In these individuals, serum cortisol was suppressed at T = 48 h to less than 50 nmol/liter on completion of the standard LDDST, but at T = 50 h + 15 after CRH, serum cortisol was greater than 38 nmol/liter. All subjects within this subgroup underwent repeat testing 3–6 months later, and all subsequently demonstrated adequate suppression of serum cortisol after both an LDDST and LDDST-CRH test without any intervention. Furthermore, during follow-up of these individuals, there was no progression of Cushingoid features.

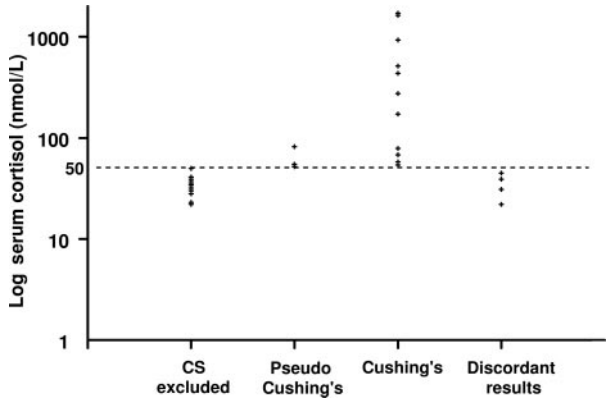

FIG. 1. Serum cortisol on completion of standard LDDST (T = 48 h) in subjects with Cushing's syndrome, subjects with pseudo-Cushing's states, and CS-excluded subjects. A serum cortisol value of 50 nmol/liter or less (*dashed line*) excluded Cushing's syndrome.

The sensitivity, specificity, and positive and negative predictive values for the LDDST and LDDST-CRH test are shown in Table 3. Using a cutoff of 38 nmol/liter as described in the original studies (10, 11), the LDDST-CRH test appeared to be less specific than the LDDST, although this did not reach statistical significance ($P = 0.06$). However, receiver operating characteristic analysis indicated that using a cutoff of 50 nmol/liter produced the best sensitivity and specificity for the LDDST-CRH test. Nevertheless, when using this cutoff (50 nmol/liter) for the LDDST-CRH test, diagnostic accuracy did not differ from that of the standard LDDST ($P = 1.0$).

Discussion

The absence of a single gold standard test makes the diagnosis of Cushing's syndrome problematical. The current

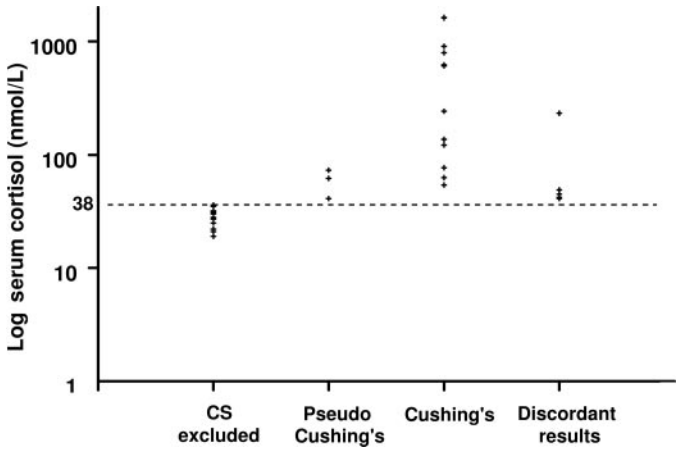

FIG. 2. Serum cortisol on completion of LDDST-CRH test (T = 50 h + 15) in subjects with Cushing's syndrome, subjects with pseudo-Cushing's states and CS-excluded subjects. A serum cortisol value of less than 38 nmol/liter (*dashed line*) excluded Cushing's syndrome.

TABLE 2. Clinical features of subjects with discordant results on LDDST and LDDST-CRH testing

Subject	Sex	Proximal myopathy	Bruising	Thin skin	Striae	Central weight gain	IGT/DM	High BP	Hirsute	Menstrual irregularity
32	F	N	N	N	N	Y	Y	N	N	N
33	F	N	N	N	N	N	Y	Y	N	Y
34	F	N	N	N	N	Y	N	N	N	Y
35	M	N	N	N	N	Y	N	Y		
36	F	N	N	N	N	Y	Y	N	Y	N

Subject numbers correspond to Table 1. Y indicates a feature is present, and N indicates a feature is absent. Characteristics of those subjects with pseudo-Cushing's or in CS-excluded subjects are given in supplemental Table 2. BP, Blood pressure; F, female; IGT/DM, impaired glucose tolerance/diabetes mellitus; M, male.

favored diagnostic strategy uses a combination of preoperative clinical criteria, radiological and endocrine investigations, and postoperative histological examination to confirm the diagnosis. Therefore, because the correct preoperative diagnosis may be both costly and time consuming, significant emphasis is placed on endocrine tests that confer high diagnostic accuracy. Our findings show that although the standard LDDST and LDDST-CRH test have equally high sensitivity in the diagnosis of Cushing's syndrome, the LDDST-CRH test is less specific. Because all subjects with Cushing's syndrome failed to suppress serum cortisol using the standard LDDST protocol, the addition of CRH to the LDDST did not confer any additional diagnostic benefit. Furthermore, in several cases, the addition of CRH actually resulted in unnecessary repeat testing in those in which the standard LDDST excluded Cushing's syndrome. Our data are not in keeping with an earlier study proposing that that the dexamethasone-suppressed CRH stimulation test accurately differentiates between pseudo-Cushing's and Cushing's syndrome with 100% sensitivity and specificity (10). However, it is important to note that the current study involved a smaller number of subjects with Cushing's syndrome. Nevertheless, another group (13) has also recently suggested that the dexamethasone-suppressed CRH test may be less accurate than originally reported in distinguishing pseudo-Cushing's states from Cushing's syndrome.

Specific differences between the current study and the original description of the dexamethasone-suppressed CRH test by Yanovski *et al.* (10) should be considered before making direct comparisons between both studies. First, in the original study, participants with either pseudo-Cushing's or Cushing's syndrome had biochemical evidence of mild hypercortisolism, as evidenced by elevated urinary free cortisol excretion. However, in the current study, subjects were included on clinical evidence alone. Second, in the original study, the majority of pseudo-Cushing's patients had an underlying psychiatric diagnosis rather than morbid obesity with obstructive sleep apnea or alcohol excess as in the current study. Furthermore, there are significant differences in the current protocol compared with the original description of the dexamethasone-suppressed CRH stimulation test. First, we administered 0.5 mg dexamethasone at 6-hourly intervals starting at 0900 h. This contrasts with the original protocol, whereby dexamethasone administration commenced at 1200 h. In addition, we used human-sequence CRH at a dose of 100 μg compared with the original protocol, which used ovine-sequence CRH adjusted according to body weight. Ovine-sequence CRH has been reported as a more potent stimulus for ACTH and cortisol release compared with human-sequence CRH (14). Therefore, in the current protocol, using human-sequence CRH, a less effective stimulus for ACTH and hence, cortisol secretion, should actually increase the specificity of our test. Despite this, the specificity of 67% using our version of the LDDST-CRH test was less than the previously reported 100% specificity (10). Similarly, in the original protocol, iv CRH was administered 2 h after the eighth dose of dexamethasone, whereas our protocol included a ninth dose of dexamethasone 2 h before CRH injection. Because subjects with pseudo-Cushing's are reported to remain sensitive to suppression by exogenous glucocorticoids, this additional dose of dexamethasone may have been expected to increase the specificity of the LDDST-CRH test using our protocol. The RIA used to measure serum cortisol in the current study also differs from that used previously. Nevertheless, despite these differences in the LDDST-CRH test protocols, the LDDST-CRH test was not superior to the standard LDDST in the diagnosis of Cushing's syndrome even when using a cutoff of 50 nmol/liter.

The dexamethasone-suppressed CRH stimulation test (10, 11) uses a serum cortisol cutoff of 38 nmol/liter. This is close to the sensitivity limits of many commercially available cortisol assays. The possibility of high assay variation at low cortisol concentrations suggests that the sensitivity of the assay used is critical to the predictive power of the dexamethasone-suppressed CRH stimulation test. The Nichols cortisol assay used in our laboratory has a functional sensitivity of approximately 15 nmol/liter, suggesting sufficient sensitivity of this assay at cortisol concentrations near the cutoffs

TABLE 3. Comparison of the LDDST and LDDST-CRH test in the diagnosis of Cushing's syndrome

	LDDST (%)	LDDST-CRH cutoff 38 nmol/liter (%)	LDDST-CRH cutoff 50 nmol/liter (%)
Sensitivity	100 (74–100)	100 (74–100)	100 (74–100)
Specificity	88 (68–97)	67 (45–84)	88 (68–97)
Positive predictive value	80 (52–96)	60 (36–81)	80 (52–96)
Negative predictive value	100 (84–100)	100 (79–100)	100 (84–100)

Specificity, sensitivity, and positive and negative predictive values were calculated using cutoff values for serum cortisol of 50 nmol/liter at 48 h (LDDST, column 2), 38 nmol/liter (LDDST-CRH test, column 3) 15 min after CRH administration, 50 nmol/liter 15 min after CRH administration (LDDST-CRH test, column 4). The 95% confidence interval for each estimate is shown in *parentheses*.

of the LDDST and LDDST-CRH tests (50 and 38 nmol/liter, respectively).

It is important to note that dexamethasone clearance may be impaired in individuals with Cushing's syndrome (8, 9). Furthermore, marked variation in serum dexamethasone levels occurs in both normal subjects and those with Cushing's syndrome after oral administration of dexamethasone (15). In this regard, the very dramatic post-CRH cortisol value observed in one of the subjects in the current study (subject 33, 233 nmol/liter) may reflect interindividual variation in dexamethasone metabolism, although this is less likely because both tests were completed on the same day. Therefore, it would have been interesting to measure dexamethasone levels in all individuals studied to assess whether this contributed to elevated cortisol levels after CRH.

In conclusion, in this small study, we have not found the LDDST-CRH test to be superior to the standard LDDST in either the diagnosis of Cushing's syndrome or differentiating between pseudo-Cushing's and Cushing's syndrome. Using our protocol, the LDDST-CRH had a lower specificity than previously described (10, 11). In addition, a number of individuals in which a standard LDDST had excluded Cushing's syndrome underwent additional unnecessary testing because of false-positive results using the LDDST-CRH test.

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