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Letters to the Editor

Dexamethasone-Suppressed Corticotrophin-Releasing Hormone–Stimulation Test Does Not Reliably Diagnose or Predict Recurrence of Cushing Disease

To the Editor:

First-line treatment for Cushing disease is surgical removal of the adrenocorticotrophin-secreting pituitary tumor. Because of the high risk of relapse, it is essential that patients receive long-term postoperative follow-up for disease recurrence through expert clinical evaluation and biochemical assessment of hypercortisolism, including the use of dexamethasone suppression *(1)*. However, no gold-standard test has been shown to accurately predict recurrence *(1)*. The dexamethasone-suppressed corticotropin-releasing hormone–stimulation (LDDST-CRH)[1] test was initially proposed to be more accurate in confirming hypercortisolism than the standard low-dose dexamethasone-suppression test (LDDST) for the diagnosis of Cushing syndrome *(2)*. The underlying principle of this test is that patients with true hypercortisolism demonstrate suboptimal cortisol suppression by dexamethasone, yet remain responsive to exogenous CRH. More recent studies have challenged the diagnostic accuracy of this test in the diagnosis of Cushing syndrome by demonstrating suboptimal specificity *(3–5)*. The utility of the LDDST-CRH test for postoperative surveillance in patients with previously diagnosed Cushing disease who have been treated with transsphenoidal hypophysectomy has not been assessed. Therefore, we investigated the performance of the LDDST-CRH test in this setting.

We identified a subset of 21 patients who had undergone pituitary surgery for Cushing disease and had remained at our center for postoperative surveillance. Each patient had undergone at least 1 postoperative LDDST and LDDST-CRH test as previously described *(3)*. Tests were performed at different time intervals after surgery. Any patients receiving hydrocortisone replacement at the time of this investigation had a 16-h interval between the last dose of hydrocortisone and the first dexamethasone dose. Until March 2006, cortisol was measured by using the Nichols Advantage 1-site chemiluminescence cortisol assay (Nichols Institute Diagnostics). In our laboratory the functional sensitivity estimated from an imprecision profile performed with Nichols reagents was 15 nmol/L *(3)*. Because of the withdrawal of the Nichols Advantage cortisol assay, from March 2006 onward cortisol was measured by using the Immulite® 2000 cortisol assay (Siemens Medical Solutions Diagnostics). The functional sensitivity of the cortisol assay in our laboratory with the use of Siemens reagents was 27 nmol/L. Disease recurrence was confirmed by the development over time of clinical features that aroused suspicion of hypercortisolism, in conjunction with a failed LDDST, as defined by a serum cortisol >50 nmol/L at time = 48 h. The absence of clinical features of hypercortisolism and suppression of serum cortisol to ≤50 nmol/L after LDDST confirmed disease remission. At the completion of the LDDST-CRH test, a serum cortisol result of <38 nmol/L was considered to exclude disease recurrence *(3)*. For those patients who passed the LDDST (cortisol ≤50 nmol/L) but failed the LDDST-CRH test (cortisol >38 nmol/L), adequate suppression of serum cortisol on completion of at least 1 subsequent LDDST was required to confirm remission, along with documented lack of evolving clinical features of Cushing disease.

No patients suffered relapse in the first 6 months postoperatively, and the mean (SD) duration of follow-up was 6.9 (1.3) years. Data for the patient cohort are shown in Table 1. During long-term follow-up, 6 patients (28%) developed recurrent disease. Among these patients, 4 demonstrated failure to suppress serum cortisol adequately to <38 nmol/L after an LDDST-CRH test, despite results showing suppression to ≤50 nmol/L during an LDDST (group 1). In these 4 patients, recurrence of Cushing disease was detected at a mean time of 10.8 (3.7) months earlier by the LDDST-CRH test than the LDDST test.

There were 15 remaining patients who did not develop clinically observed recurrent hypercortisolism, and the diagnosis of remission was supported by suppression of serum cortisol to ≤50 nmol/L after an LDDST. Eight of these patients showed failure to suppress serum cortisol adequately to <38 nmol/L after an LDDST-CRH test (group 3). All 8 patients were still in clinical remission at the time of this report, and furthermore, these patients underwent a subsequent LDDST that confirmed adequate cortisol suppression to ≤50 nmol/L. Therefore, the LDDST-CRH test had a diagnostic specificity of 47% for excluding recurrent Cushing disease. Interestingly, of these 8 patients with a false-positive LDDST-CRH test result, 5 passed a subsequent LDDST-CRH test without any clinical intervention. These patients have remained in remission for a mean period of 107 (24.3) months. This disease-free period is comparable

[1] Nonstandard abbreviations: LDDST-CRH, dexamethasone-suppressed corticotropin-releasing hormone–stimulation; LDDST, low-dose dexamethasone-suppression test.

to that seen in the patients in group 4, who have displayed adequate cortisol suppression detected by use of both tests and have remained in clinical and biochemical remission for a mean period of 102 (29.8) months.

This study is the first to assess the use of the LDDST-CRH test as a predictor of recurrence of Cushing disease in patients previously treated by pituitary surgery. The performance of this test is consistent with preoperative studies demonstrating suboptimal specificity for the diagnosis of Cushing syndrome *(3–5)*. Our results suggest that this test is not an accurate predictor of recurrence and in fact may promote unnecessary, more intense surveillance. Therefore, we do not advocate the routine use of the LDDST-CRH test for the detection of recurrent hypercortisolism in patients who have undergone pituitary surgery for Cushing disease.

Table 1. Summary of LDDST-CRH and LDDST results and time spent in remission for 21 patients who underwent follow-up after pituitary surgery for Cushing disease.

Patient	Time after surgery, months	Serum cortisol, nmol/L	
		On completion of LDDST	On completion of LDDST-CRH
Group 1: LDDST-CRH test failed to predict subsequent recurrence of Cushing disease			
1	1	<30	68
	5	<30	98
	11	41	177
	16	40	215
	19	107	268
2	1	35	178
	4	95	370
3	80	<30	69
	89	95	213
4	4	46	38
	12	34	89
	18	100	n/a[a]
Group 2: Recurrence of Cushing disease confirmed by LDDST and LDDST-CRH at first assessment			
5	10	249	516
6	13	53	70
Group 3: Failed LDDST-CRH test, but in disease remission when assessed clinically and by LDDST			
7	15	43	34
	28	50	52
	41	36	40
	53	32	30
8	83	<30	46
	106	<30	<30
9	1	32	39
	14	<30	<30
	34	<30	<30
10	99	<30	165
	110	<30	<30
11	66	33	94
	84	<30	187
	98	<30	<30
12	48	31	33
	66	<30	87
	72	<30	201
	78	<30	140

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Table 1. Summary of LDDST-CRH and LDDST results and time spent in remission for 21 patients who underwent follow-up after pituitary surgery for Cushing disease. (*Continued from page XX*)

Patient	Time after surgery, months	Serum cortisol, nmol/L	
		On completion of LDDST	On completion of LDDST-CRH
13	3	<30	220
	4	<30	n/a
	10	n/a	122
	14	50	183
14	159	41	57
	182	<30	54
Group 4: Remained in clinical remission and passed LDDST and LDDST-CRH[b]			
15	71	<30	<30
16	30	<30	n/a
	38	<30	<30
17	23	35	36
18	114	33	36
19	1	31	31
20	4	<30	<30
21	47	<30	<30

[a] n/a, Test result not available.
[b] For an LDDST, pass is taken as suppression of serum cortisol to ≤50 nmol/L and for a LDDST-CRH test, suppression to <38 nmol/L.

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