A Combined Dexamethasone Desmopressin Test as an Early Marker of Postsurgical Recurrence in Cushing’s Disease

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Context: Recurrence of Cushing’s disease (CD) after transsphenoidal surgery (TSS) occurs in about 25% of cases. Twenty percent of patients with immediate postsurgical corticotroph deficiency will present late recurrence.

Objective: The aim of the study was to evaluate a coupled dexamethasone desmopressin test (CDDT) as a predictor of recurrence of CD.

Design: We conducted a prospective bicenter study (Marseille and Grenoble, France).

Patients: We studied 38 patients treated by TSS for CD with a mean follow-up of 60 months.

Intervention(s): We evaluated 24-h urinary free cortisol, ACTH, and cortisol plasmatic levels and performed low-dose dexamethasone suppression test and CDDT 3 to 6 months after surgery and then yearly.

Main Outcome Measures: After CDDT, ACTH ratio (ACTHr) was defined as (PeakACTH – BaseACTH)/BaseACTH. Cortisol ratio (Cortisolr) was defined as (PeakCortisol – BaseCortisol)/BaseCortisol. Basal values were observed after low-dose dexamethasone suppression test. Receiver operator characteristics curve defined ACTHr and Cortisolr giving the best sensitivity and specificity associated with recurrence.

Results: Ten patients presented recurrence. ACTHr and Cortisolr were superior or equal to 0.5 in all patients with recurrence and in three of 28 patients in remission (100% sensitivity, 89% specificity). The test became positive in eight of 10 patients with recurrence 6–60 months before classical markers of hypercortisolism. Six patients with immediate postsurgical corticotroph deficiency presented recurrence. All of them presented CDDT positivity during the 3 yr after surgery, and recurrence 6 to 60 months after CDDT positivity.

Conclusions: CDDT is an early predictor of recurrence of CD and could be of particular interest in the first 3 yr after surgery, by selecting patients at high risk of recurrence despite falsely reassuring classical hormonal markers. (J Clin Endocrinol Metab 94: 1897–1903, 2009)
First-line treatment of Cushing’s disease (CD) is transsphenoidal surgery (TSS), because no medical treatment definitively cures the disease (1). Surgical remission is obtained in 50 to 80% of cases, mainly depending on adenoma localization and neurosurgeon experience (2–5). Recent data suggest that the risk of recurrence after surgery is closer to 30% than to the previously estimated 20% of cases; the risk was probably underestimated based on studies with short-term follow-up, not exceeding 4 yr (6, 7).

There are currently no ideal predictive markers of recurrence (1, 8). Many studies suggested that immediate postsurgical cortisol levels below 50–80 nmol/liter were good prognosis markers (2, 9–12). Despite this criterion, however, about 20% of patients with immediate corticotroph deficiency will present delayed recurrence (6, 13, 14). Prognostic value remains controversial for other markers such as pathological analysis (15) or hyperresponsiveness to CRH or metyrapone test (16, 17). A recent study reported promising results based on midnight salivary cortisol (18). However, due to the lack of sufficient confirmative data, long-term follow-up remains necessary in all surgically treated patients.

Desmopressin stimulation test is currently used as an equivalent of CRH in petrolos sinus sampling (19, 20) or to differentiate pseudo-Cushing from Cushing’s syndrome (21). We and others had previously shown that desmopressin test could be a valuable predictor of long-term recurrence in surgically treated CD (22–25). Desmopressin stimulates V3 receptors in corticotroph adenomatous cells (26, 27). Increased levels of ACTH and cortisol after desmopressin stimulation suggest the presence of residual adenomatous cells, whereas the lack of response indicates complete resection (22, 23, 25). However, in a few cases, nonadenomatous cells induce a slight increase in ACTH and cortisol levels, making it difficult to interpret the test. Low-dose dexamethasone suppression test (LDDST) is an effective tool for positive CD diagnosis (1). Coupling dexamethasone suppression with desmopressin stimulation test should theoretically be of interest because only residual corticotroph cells would be stimulated.

In this study, we prospectively evaluated the value of a coupled dexamethasone desmopressin test (CDDT) as a predictor of recurrence in CD.

**Patients and Methods**

**Diagnosis of CD**

Between 1998 and 2008, 48 patients with CD treated by TSS presenting with immediate postsurgical remission were prospectively evaluated by the CDDT in two French tertiary referral centers: La Timone Hospital (Marseille, France) and Grenoble Hospital (Grenoble, France). After exclusion of 10 patients who had a follow-up inferior to 18 months at the end of the study, 38 patients were available for the present analysis. The diagnosis of CD was based on the combination of clinical features of hypercortisolism and biochemical assessment according to recommended guidelines (28). All but two patients had positive presurgical magnetic resonance imaging (MRI) (both were considered as having microadenomas not visualized on MRI). Patients were then treated surgically. Histological confirmation of CD was reported in 30 patients (79%).

**Post surgical evaluations**

All patients had immediate (d 3 to 7) postsurgical ACTH and plasma cortisol evaluations (every 4 h during 24 h) and 24-h urinary free cortisol (UFC), except in case of signs of adrenal crisis. In this case, hydrocortisone supplementation was initiated after a single ACTH and cortisol determination. All 38 patients had immediate remission after surgery. This cohort was divided into patients who had severe immediate postsurgical corticotroph deficiency (defined by 0800 h cortisol level <80 nmol/liter or signs of adrenal crisis during d 1 to 5 after surgery) and those without corticotroph deficiency. Each patient had the same evaluation with an LDDST 3 to 6 months after surgery and then yearly. In patients treated by hydrocortisone, evaluation was performed 48 h after withdrawal of the drug.

Patients were considered in remission when at least one of the three following criteria was met: 1) normalized 24-h UFC at three consecutive samplings; 2) maintained nycthemeral ACTH and cortisol rhythms; 3) or suppressed cortisol level after LDDST (<50 nmol/liter). Recurrence was defined as the presence of these three abnormal criteria. We also determined the time elapsed between surgery and the first time each individual parameter were in favor of recurrence, i.e. elevated 24-h UFC, lack of nycthemeral ACTH and cortisol rhythms, or unsuppressed cortisol level after LDDST (>50 nmol/liter).

**CDDT**

The test consisted of 1 mg dexamethasone given at 0000 h, determination of ACTH and cortisol samples at 0800 h (similar to a LDDST) followed by a 10-μg iv desmopressin injection. ACTH and cortisol samples were obtained before injection and then 15, 30, 60, 90, 120, and 180 min after injection. The CDDT was performed at each follow-up evaluation, 48 h after hydrocortisone withdrawal if patients were treated. We evaluated the percentage increase in ACTH and cortisol between samplings at 0800 h after dexamethasone test and sampling corresponding to the peak after desmopressin test. This increase ratio was defined as (PeakACTH − BaseACTH)/BaseACTH for ACTH ratio (ACTHr), and (PeakCortisol − BaseCortisol)/BaseCortisol for cortisol ratio (Cortisolr). Baseline ACTH and cortisol were values obtained after LDDST (also corresponding to t0 of desmopressin test); peak ACTH and cortisol were maximal values obtained after desmopressin injection at one of the six samplings performed.

**Assay and sample methods**

In Marseille, plasma ACTH, cortisol, and UFC were measured by commercial RIA kits (Beckman-Coulter-Immunotech, Marseille, France). The ACTH immunoradiometric assay had a sensitivity of 1.2 pg/ml (at 95% probability). The cortisol assay had a sensitivity of 10 nmol/liter. In Grenoble, plasma ACTH was measured by Brahms commercial RIA kit, with a sensitivity of 2.4 pg/ml (at 95% probability). The plasma cortisol was measured by Modular-Roche automat (Roche Diagnostics, Basel, Switzerland), with a sensitivity of 8 nmol/liter. UFC assay had a sensitivity of 10 nmol/liter. Abnormal cortisol circadian rhythm was defined for each investigator by lack of falling cortisol levels during the day after 0800 h peak as previously defined (29). Abnormal ACTH circadian rhythm was defined by persistently elevated ACTH levels despite elevated cortisol levels (29).

**Statistical analysis**

We used a receiver operator characteristics (ROC) curve to determine which ACTHr and Cortisolr gave the best sensitivity and specificity to detect the patients who presented recurrence. The ROC curve analysis was performed at the time when the criteria for recurrence were present in each particular patient. Time that elapsed between surgery and first abnormal response to CDDT was noted and compared with the period of first onset of positivity of other markers of hypercortisolism as previously defined. Statistical analysis was per-
TABLE 1. Individual data of patients in remission (n = 28)

| Patient no. | Sex/age (yr) | Macro-or microadenoma | Follow-up (months) | Corticotroph deficiency | ACTHr/Cortisolr |
|-------------|--------------|------------------------|--------------------|-------------------------|-----------------|
| 1           | F/35         | m                      | 24                 | Yes                     | 0.0/0.5         |
| 2           | F/32         | m                      | 60                 | Yes                     | 3.6/12.7        |
| 3           | F/42         | m                      | 84                 | Yes                     | 0.0/0.1         |
| 4           | F/32         | m                      | 60                 | Yes                     | 0.0/0.2         |
| 5           | F/56         | m                      | 60                 | Yes                     | 0.0             |
| 6           | F/50         | m                      | 60                 | Yes                     | 0.5/0.2         |
| 7           | F/36         | m                      | 24                 | Yes                     | 1.7/6           |
| 8           | F/52         | m                      | 24                 | Yes                     | 0.0/0.1         |
| 9           | F/31         | m                      | 24                 | Yes                     | 0.2/0.3         |
| 10          | M/32         | m                      | 96                 | Yes                     | 0.0/0.1         |
| 11          | F/42         | m                      | 24                 | Yes                     | 0.0/0.5         |
| 12          | M/49         | m                      | 36                 | Yes                     | 0.0/0.3         |
| 13          | F/35         | m                      | 24                 | Yes                     | 0.0             |
| 14          | F/35         | M                      | 48                 | Yes                     | 0.0             |
| 15          | F/29         | m                      | 36                 | Yes                     | 0.0/0.3         |
| 16          | F/42         | m                      | 48                 | Yes                     | 0.0/0.0         |
| 17          | F/39         | m                      | 84                 | Yes                     | 0.0/0.7         |
| 18          | F/68         | m                      | 120                | Yes                     | 0.0/0.1         |
| 19          | M/56         | m                      | 120                | Yes                     | 0.0/0.1         |
| 20          | F/45         | m                      | 84                 | Yes                     | 0.3/0.3         |
| 21          | F/26         | m                      | 72                 | Yes                     | 0/0             |
| 22          | F/46         | M                      | 108                | No                      | 0.1/0           |
| 23          | F/46         | M                      | 24                 | No                      | 1.2/0           |
| 24          | F/56         | m                      | 24                 | No                     | 0.0/0.1         |
| 25          | F/57         | m                      | 36                 | No                      | 0.0/0           |
| 26          | F/67         | M                      | 96                 | No                      | 0.4/0.2         |
| 27          | F/41         | m                      | 96                 | No                      | 0.0/0.1         |
| 28          | F/45         | m                      | 60                 | No                      | 0.0/0           |

Posturgical corticotroph deficiency was defined as low 0800 h plasmatic cortisol level (<80 nmol/liter) associated with low 24-h UFC level. ACTHr was defined as (PeakACTH − BaseACTH)/BaseACTH, with BaseACTH defined as ACTH value at 0800 h after LDDST. Cortisolr was defined as (PeakCortisol − BaseCortisol)/BaseCortisol, with BaseCortisol defined as cortisol value at 0800 h after LDDST. Patients 2, 4, and 7 had positive response to CDDT and lack of recurrence as previously defined. Sex: F, Female; M, male. Adenomas: m, microadenoma; M, macroadenoma.

TABLE 2. Individual data of patients in recurrence (n = 10)

| Patient no. | Sex/age (yr) | Micro-or macroadenoma | Follow-up (months) | Corticotroph deficiency | ACTH/cortisol increase | 24-h UFC | ACTH cortisol cycle | LDDST | CDDT |
|-------------|--------------|-----------------------|--------------------|-------------------------|------------------------|---------|-------------------|--------|------|
| 1           | F/29         | m                      | 18                 | Yes                     | 6/25.1                 | 18      | 18                | 18     | 12   |
| 2           | F/32         | M                      | 108                | Yes                     | 1.1/5.2                | 96      | 72                | 84     | 36   |
| 3           | F/27         | M                      | 96                 | Yes                     | 2.1/4.8                | 72      | 72                | 72     | 24   |
| 4           | F/22         | m                      | 24                 | Yes                     | 2.2/2.5                | 24      | 24                | 24     | 6    |
| 5           | F/32         | M                      | 96                 | Yes                     | 0.6/0.6                | 84      | 72                | 72     | 36   |
| 6           | M/28         | m                      | 24                 | Yes                     | 1.3/1.2                | 24      | 24                | 24     | 12   |
| 7           | M/38         | M                      | 96                 | No                      | 3.9/4.8                | 96      | 96                | 96     | 96   |
| 8           | M/21         | m                      | 108                | No                      | 1/0.7                  | 108     | 108               | 108    | 108  |
| 9           | F/50         | M                      | 24                 | No                      | 1/2.1                | 24      | 24                | 24     | 12   |
| 10          | F/29         | m                      | 72                 | No                      | 0.5/2.5                | 36      | 36                | 36     | 12   |

Recurrence was defined as elevated 24-h UFC, loss of ACTH and cortisol nycthemeral rhythms, and unsuppressed plasma cortisol level after LDDST (>50 nmol/liter). Posturgical corticotroph deficiency was defined as low 0800 h plasmatic cortisol level (<80 nmol/liter). *, P < 0.05 in comparison with first onset of positivity of CDDT. Sex: F, Female; M, male. Adenomas: m, microadenoma; M, macroadenoma.

Results

Thirty-eight patients were prospectively followed up for a median time of 60 months (range, 18–120) (mean follow-up, 60 months). At their last follow-up, 10 patients (26%) presented clinical and biological signs of recurrence of hypercortisolism. Individual data are given in Tables 1 and 2. As shown in Table 3, mean follow-up was not statistically different between remission and recurrence groups. In contrast, patients presenting with recurrence were younger at diagnosis (P = 0.002) and more frequently had macroadenomas (P = 0.034). Initial postoperative MRI evaluation (3 months after surgery) did not show evident MRI remnant image in the patients of the cohort.

Immediate postsurgical corticotroph deficiency and rate of recurrence

As shown in Table 4, 27 patients (71%) presented immediate postsurgical corticotroph deficiency; they were therefore treated by hydrocortisone. Six of them (22%) presented recurrence after a median time of 48 months (range, 18–96) (mean, 53 months).

In contrast, 11 patients (29%) did not present corticotroph deficiency at immediate postsurgical evaluation. Four of them (40%) presented recurrence after a median time of 66 months (range, 24–108) (mean, 66 months); the seven remaining patients are still in remission after a median follow-up of 60 months (range, 24–108) (mean, 63 months).

Immediate postsurgical severe corticotroph deficiency (defined by 0800 h cortisol level <80 nmol/liter) was a good predictor of remission (78 vs. 63% of patients in remission in hypocorticolic or normocortisolic patients, respectively; P = 0.03).

CDDT is a marker of recurrence of CD

As shown in Table 3, there was a significant difference between mean ACTHr and Cortisolr between the remission and recurrence groups (P = 0.005 and P = 0.02 for ACTHr and Cortisolr, respectively).
TABLE 3. Characteristics of recurrence and remission groups

|                      | Remission (n = 28) | Recurrence (n = 10) | P  |
|----------------------|--------------------|---------------------|----|
| Mean age (yr)        | 43.7 [26–68]       | 30.8 [21–50]        | 0.002 |
| Sex ratio (F/M)      | 2/5                | 7/3                 | NS  |
| Micro/macroadenoma   | 24/4               | 4/6                 | 0.034 |
| Mean follow-up (months) | 59 [24–120]      | 66 [18–108]        | NS  |
| Mean Cortisol        | 1.16 [0–12.7]      | 4.98 [0.6–25.1]    | 0.02 |
| Mean ACTHr           | 0.31 [0–3.6]       | 1.98 [0.6–6]       | 0.005 |
| Corticotroph deficiency | 21 (75%)        | 6 (60%)             | 0.03 |

Post-surgical corticotroph deficiency was defined as low 0800 h plasmatic cortisol level (<80 nmol/liter). Minimum and maximum values are between brackets.

F, Female; M, male; NS, not significant.

TABLE 4. Characteristics of corticotroph deficiency and no corticotroph deficiency groups

|                  | Corticotroph deficiency | No corticotroph deficiency | P  |
|------------------|-------------------------|----------------------------|----|
| No. of patients  | 27                      | 11                         |    |
| Sex ratio (F/M)  | 2/3                     | 9/2                        | NS  |
| Mean age (yr)    | 39.3 [21–68]            | 43.5 [22–67]               | NS  |
| Micro/macroadenoma | 22/5                 | 6/5                        | 0.001 |
| Mean follow-up (months) | 60 [18–120]       | 61 [24–108]                | NS  |
| Remission        | 21 (78%)                | 7 (63%)                    | 0.03 |

Post-surgical corticotroph deficiency was defined as low 0800 h plasmatic cortisol level (<80 nmol/liter) during d1 to 5 after surgery. Minimum and maximum values are between brackets. F, Female; M, male; NS, not significant.

Cortisolr, respectively). Figure 1 represents combined values of the CDDT according to the final status of the patient: all of our patients with recurrence (100%) presented ACTHr and Cortisolr superior or equal to 0.5 (i.e. 50% ACTH and cortisol increase from baseline), whereas three patients in remission (10.7%) presented the same criteria. All the peak values were observed between 15 and 120 min after desmopressin injection.

We then used a ROC curve to determine the optimal values of ACTHr and Cortisolr giving the best sensitivity and specificity in remission or recurrence (Fig. 2). Taken individually, each parameter gave 100% sensitivity associated with 80% specificity when superior or equal to 0.5.

The association of the two parameters, i.e. ACTHr associated with Cortisolr superior or equal to 0.5, gave 100% sensitivity associated with 89% specificity and negative predictive value of 1. In comparison, positive predictive value was equal to 0.77. Three patients who presented ACTHr and Cortisolr superior to 0.5 were indeed in remission after a mean follow-up of 48 months (range, 24–60). They are indicated by arrows in Fig. 1. The first one had for the first time positivity of CDDT 6 months after surgery and abnormal circadian rhythm 5 yr after surgery. UFC and LDDST remained normal at this last follow-up evaluation, and the patient was thus classified as still in remission. The second one had a positive CDDT response 1 yr after surgery. His last follow-up evaluation was still normal 2 yr after surgery. The third patient had a positive CDDT response 3 yr after surgery. His last follow-up evaluation was still normal 5 yr after surgery.

Interestingly, response to CDDT remained positive during all recurring patients’ yearly follow-up evaluations. Note that CDDT became abnormal in five patients while they still presented with corticotroph deficiency.

Twenty-eight of our patients had microadenomas; four (14.2%) of them presented recurrence of their disease. They all had positive response to CDDT. In contrast, the three patients with abnormal CDDT despite remission also had microadenoma.

FIG. 1. Correlations between ACTHr and Cortisolr after coupled dexamethasone desmopressin stimulation test. ACTHr was defined as (PeakACTH − BaseACTH)/BaseACTH, with BaseACTH defined as ACTH value at 0800 h after LDDST. Cortisolr was defined as (PeakCortisol − BaseCortisol)/BaseCortisol, with BaseCortisol defined as cortisol value at 0800 h after LDDST. Association of ACTHr and Cortisolr superior or equal to 0.5 gave 100% sensitivity and 89% specificity in recognizing recurrence. Circle, Patient with recurrence; cross, patient in remission at latest follow-up. Recurrence was defined as the presence of elevated 24-h UFC associated with loss of nycthemeral ACTH and cortisol secretion, and unsuppressed cortisol level after LDDST, i.e. superior to 50 nmol/liter. Arrows indicate patients with positive response to CDDT and lack of recurrence.

FIG. 2. ROC curve based on ACTHr and Cortisolr. Dotted line, ACTHr; dashed line, Cortisolr.
Corticotroph deficiency patients with immediate severe postsurgical corticotroph deficiency

In eight of the 10 patients with recurrence of CD, positivity of CDDT was observed significantly earlier than with the other markers (P = 0.018); UFC, nycthemeral ACTH, and cortisol levels and LDDST were in favor of recurrence after a median time of 54 months, compared with CDDT, for which response was positive after a median time of 18 months (mean time of 58 vs. 35 months, respectively) as shown in Table 2. CDDT became positive 6 to 60 months before biological CD markers. The two remaining patients had late recurrence of their CD (96 and 108 months after surgery), and CDDT became positive at the same time as the other markers (Fig. 3).

CDDT is an early and effective marker of recurrence in patients with immediate severe postsurgical corticotroph deficiency

As shown in Table 2, six of our 10 patients with recurrence presented with immediate postsurgical corticotroph deficiency (0800 h cortisol > 80 nmol/liter). All of them had ACTHr and Cortisolr greater than 0.5 during the first 3 yr after surgery. They presented CD recurrence 6 to 60 months after CDDT positivity. In contrast, in the four patients without immediate postsurgical corticotroph deficiency, two with late recurrence (96 and 108 months after surgery) did not present any difference between time to positivity of CDDT and other markers; the two other patients with early recurrence (24 and 26 months after surgery) presented positivity to CDDT 12 and 24 months between biological recurrence defined by classical markers.

Example of evolution of markers of hypercortisolism in a patient with recurrence (see also patient 2 on Table 2)

Patient 2 was aged 32 yr when CD was diagnosed in Marseille. She was treated by TSS and had severe immediate post-surgical corticotroph deficiency that necessitated hydrocortisone replacement therapy for 18 months. Three years after surgery, she presented positive response to CDDT (ACTHr was 1.1, Cortisolr was 5.2); this response remained positive during all subsequent yearly evaluations. Six years after surgery, she presented lack of ACTH and cortisol rhythms. No treatment was initiated because of the lack of clinical signs of hypercortisolism, normal UFC, and suppressed cortisol level after LDDST. Seven years after surgery, cortisol was not suppressible after LDDST (64 nmol/liter). Eight years after surgery, she eventually presented clinical signs of hypercortisolism associated with increased 24-h UFC (250 nmol/24 h) and was treated by bilateral adrenalectomy because no image of adenoma was visible on pituitary MRI.

Discussion

The rationale for using the desmopressin test was based on previous reports showing that desmopressin was able to stimulate ACTH release in CD patients but not in normal subjects (24–26, 30). However, even if desmopressin theoretically stimulates only adenomatous corticotroph cells as they express V2-V3 receptors (27, 31), the imperfect accuracy of the desmopressin stimulation test suggests that a few nonadenomatous corticotroph cells might be stimulated by desmopressin. We had indeed previously shown that the desmopressin stimulation test could be a predictive factor of recurrence but that this test had 80% sensitivity and specificity (22). A recent study based on 57 patients confirmed the interest of the desmopressin test as an early predictive factor of recurrence, despite low sensitivity (33%) (23). Taking into account the fact that the LDDST was theoretically able to inhibit all nonadenomatous corticotroph cells (1), we decided to combine both tests. The results of the CDDT are promising in detecting recurring CD: 100% sensitivity, 89% specificity, and a predictive negative value of 1. Positive predictive value was only 0.77 because three patients in remission had positive response to our CDDT, after a mean follow-up of 48 months. This might be due to the short interval between positivity of CDDT and last follow-up evaluation in two patients. For these three patients, the next follow-up evaluations should provide appropriate information on their final corticotroph status.

Our data support the hypothesis that the CDDT could be an early predictive factor of recurrence. The test became indeed positive 6 to 60 months before classical markers of recurrence (Fig. 3). Desmopressin response of remnant adenomatous cells could thus be observed before these cells began secreting detectable ACTH levels because nonadenomatous corticotroph cells are suppressed by LDDST. An interesting point about the CDDT is that it remained constantly positive at subsequent follow-up evaluations in all of our patients with positive response, thus allowing us to not necessarily repeat the test after first positive response. This point is of importance because it is well known that variable hormonogenesis is frequent during CD, making baseline evaluation of urinary or cortisol parameters sometimes unreliable. Note that eventually two patients presenting with very late recurrence (8 and 9 yr) had response to CDDT at the
same time as classical markers. These patients had nonsymptomatic CD and moderately elevated urinary and plasma cortisol levels. We hypothesize that tumor growth, and as a consequence cell response to the test, were not sufficient to induce an early detectable response to desmopressin. CDDT is therefore probably of interest within the first 3 yr because 80% of recurring patients responded to desmopressin in that postoperative period.

Our data confirmed that immediate postsurgical severe corticotroph deficiency was a good predictor of long-term remission. However, as also reported in a large cohort of operated patients with CD (6), about 20% of patients with this criterion presented recurrence. All of them had early response to the CDDT during the first 3 yr of their postoperative evaluations. CDDT early response could allow selection of the 20% of patients at risk of recurrence despite immediate severe postsurgical corticotroph deficiency, which would lead to a closer follow-up. In contrast, in seven of our patients in remission despite postsurgical immediate cortisol level superior to 80 nmol/liter, CDDT remained negative after a mean period of 63 months. However, two of our patients with very late recurrence and lack of postsurgical corticotroph deficiency presented positivity of CDDT in the same period as other classical markers; we cannot currently be sure that the seven patients in remission with lack of postsurgical corticotroph deficiency will not present late recurrence. As a consequence, it is not possible to say that CDDT could allow selection of patients at low risk of recurrence despite postsurgical eucortisolic state.

There are some potential limitations to our study. The use of distinct hormone assays is circumvented by reference to the normal range defined for each assay and by the use of ratios to define positivity of CDDT. Secondly, our study concerned a relatively small number of patients. We decided to limit the study to patients with a sufficiently prolonged follow-up to avoid the risk of undiagnosed late recurrences. Another point is the lack of available data on the CDDT preoperatively. We decided not to include these data because the aim of our study was to try to define an optimal way to select patients at high risk of recurrence postsurgically, and not to define a new marker of diagnosis of hypercortisolism. Because all our patients were considered in remission postoperatively and because recurrence was defined by classical biological markers and not by the CDDT, we think that these partial data would have been of limited interest. However, it is admitted that approximately 20% of patients with active CD show no response to desmopressin injection. Performing a desmopressin test before surgery would thus probably avoid the risk of falsely reassuring a negative test in nonresponder patients in postsurgical follow-up. The last point concerns the fact that some patients with active CD could have preserved LDDST, which could bias our definition of remission. We decided to choose the strictest criteria of remission to avoid a risk of an erroneous diagnosis of recurrence. There was no discrepancy between our results and the recurrence status if we only took into account two instead of three parameters (i.e., excluding LDDST). Moreover, as shown in Table 1, none of our patients presented positive UFC and loss of nycthemeral rhythm before LDDST positivity, thus excluding the possibility that the early onset of positivity of our test was due to a bias in the definition of recurrence.

The superiority of the coupled test in comparison with the desmopressin test remains to be proven because our study is the first one to evaluate the CDDT. A recent study on desmopressin test reported very low sensitivity, estimated to be equal to 33% of cases, and high specificity equal to 100% of cases (23). Because our study was based on CDDT repeatedly performed during the follow-up period of operated patients, whereas that study was based on a single desmopressin test performed in the immediate postoperative period, results are difficult to compare. The interest of LDDST before desmopressin test theoretically consists in increasing this sensitivity by blocking normal corticotroph cells. Even if dexamethasone could at least also partly suppress remaining adenomatous corticotroph cells and thus delay the response to the test, we think that it is worth trying to detect only patients at risk of recurrence rather than having a high number of false-positive patients. However, because the majority of our patients with recurrence had positivity onset of the test at least 1 yr after surgery, we do not think that this potential partial blockade of corticotroph remnant by dexamethasone could be a major problem in delaying the response to CDDT.

We propose that a follow-up algorithm in the lack of immediate postsurgical failure should therefore include CDDT (with 15- to 120-min samplings) as follows:

- In patients with immediate severe postsurgical corticotroph deficiency, CDDT should be performed with 24-h UFC, plasma ACTH/cortisol samples, and LDDST at 3 to 6 months and then yearly for 3 yr after surgery. In the lack of CDDT-positive response in these patients considered at lower risk, late recurrence is highly improbable and monitoring should be only clinical. In case of positivity of CDDT (0.5-fold or more increased ACTHr and Cortisolr), patients are at risk of recurrence in the next 60 months and should be closely monitored with classical markers of hypercortisolism. The CDDT could thus be interesting either to reassure physicians in case of a negative test or to perform adequate prolonged follow-up in case of a positive test, thus allowing treatment of the recurrence as soon as it begins.

- In patients considered at high risk of recurrence due to immediate postsurgical cortisol levels above 80 nmol/liter, the use of CDDT is less evident. It could help select patients at low risk of recurrence despite this criterion. However, because those two of our patients with late recurrence presented concomitant positivity of CDDT and other classical markers, we are not sure that negative CDDT brings sufficient information to stop the follow-up.

To conclude, this report is the first to evaluate a CDDT in the postsurgical follow-up evaluation of patients with CD. It proved of interest as an early marker of recurrence of CD because it became positive 1 to 4 yr before the classical markers of hypercortisolism, thus allowing early selection of patients at high risk of recurrence, particularly in case of postsurgical corticotroph deficiency. It then can serve to propose an appropriate and close follow-up. Although our study is limited by a small number of patients and a relatively short follow-up, our results show the...
need for future studies to confirm that CDDT could represent a valuable tool in the follow-up of CD.

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