The desmopressin test as a predictive factor of outcome after pituitary surgery for Cushing’s disease

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Abstract
Objective: Taking advantage of the over-expression of V3 receptors in adenomatous corticotroph cells, we evaluated the response to the vasopressin agonist desmopressin in 22 patients operated on for Cushing’s disease, with a mean follow-up of 4.5 years.

Subjects and methods: Twenty-two patients (17 women) operated on for Cushing’s disease with a follow-up > 2 years (median, 48; range, 24–141 months) underwent one desmopressin test (10 µg i.v. bolus) 3–6 months postoperatively. Twelve were in remission (R group), five had immediate failure (IF) after surgery and five had late recurrence (LR).

Results: Both ACTH and cortisol peaks after desmopressin were significantly lower in the R group than in the LR group (P = 0.003 and P = 0.013 respectively). The receiver operator characteristic curve method defined an ACTH peak threshold ≥ 22 pg/ml or ACTH rise ≥ 35%; cortisol peak ≥ 350 nmol/l or cortisol rise ≥ 14%. None of twelve patients in remission had ACTH or cortisol peaks above these thresholds vs three of five patients from the LR group and five of five in the IF group.

Discussion: On the basis of ACTH or cortisol peaks respectively, the desmopressin test was predictive of a later recurrence with a positive predictive value of 100% or 80% respectively, and a negative predictive value of 92%. Sensitivity and specificity were 80% and 100% respectively based on ACTH peak, and 80% and 92% respectively based on cortisol peak.

Conclusion: In this first long-term study, a marked response of ACTH or cortisol to desmopressin was predictive of a later recurrence with good specificity and sensitivity.
for Cushing’s disease in a single center, with a mean duration of follow-up of 4.5 years, and at least 2 years after surgery. In this first long-term study, we found that a marked response of plasma ACTH or cortisol to desmopressin was predictive of a later recurrence with good specificity and sensitivity.

Subjects and methods

Subjects

A population of 54 patients had been operated on for Cushing’s disease in our center at least 2 years before data collection for the present study; among them 43 were available for long-term follow-up. The subset of 22 patients who had given informed consent to undergo postoperative desmopressin tests were analyzed in this study. These patients were 17 women and five men, with a mean age at diagnosis of 35 years (range, 14–57 years). The diagnosis of Cushing’s disease was established on the basis of clinical features and standard hormonal criteria: high urinary free cortisol (UFC) excretion, normal or high plasma ACTH concentration, high serum cortisol concentration with loss of cortisol nychthemeral variations and lack of suppression after a low-dose dexamethasone test (1 mg orally overnight), but adequate suppression after a high-dose dexamethasone test (8 mg/day orally for 48 h). Inferior petrosal sinus sampling for ACTH was performed only in five patients to discriminate pituitary and ectopic sources of ACTH. Desmopressin testing was not used as a routine preoperative diagnostic procedure. Nuclear magnetic resonance imaging showed a pituitary adenoma in all other patients. The diagnosis of Cushing’s disease was confirmed in 16 patients after pituitary adenomectomy, as the histological examination showed the existence of adenomatous tissue, with positive staining for ACTH at immunohistochemical analysis. In the remaining six patients, the diagnosis was confirmed by inferior petrosal sinus sampling \((n = 3)\) and/or by identification of the adenoma by the neurosurgeon \((n = 4)\).

After surgery, the patients were followed for at least 2 years (mean follow-up, 55 months; median, 49 months; range, 24–141 months) and were classified into two groups. The first group included twelve patients in remission (R group). The patients were considered to be in remission on the basis of clinical cure, a corticotroph deficiency or normalization of urinary free cortisol excretion, and resumption of plasma ACTH and serum cortisol nychthemeral variations (midnight serum cortisol less than 50 nmol/l) and, when available, a serum cortisol less than 50 nmol/l after a low-dose dexamethasone test.

The second group was comprised of ten patients who were not cured. This group was divided into two subgroups: five patients with immediate failure of surgery (IF group) and five patients with late recurrence (LR group) that was diagnosed 6, 7, 12, 18 and 36 months after surgery. The criteria for immediate failure or late recurrence were the same as those used for the diagnosis of Cushing’s disease.

Methods

In each patient, plasma ACTH and cortisol values were measured every 4 h during 24 h (0800, 1200, 1600, 2000, 2400 and 0400 h), and UFC during 24 h. These baseline ACTH and cortisol determinations were performed 6–8 days postoperatively, at 3 and 6 months, then at yearly intervals. All subjects were monitored in the neurosurgery or endocrinology departments for at least 8 days postoperatively. Some of them required early postoperative parenteral cortisol replacement therapy. In all cases, however, basal or dynamic evaluation of the pituitary adrenal axis was performed after at least 36–48 h without hydrocortisone. The most recent investigation was used for allocation into each outcome group. Plasma ACTH and cortisol, and UFC were measured by commercial radioimmunoassay kits (Beckman-Coulter-Immunotech, Marseille, France). The ACTH immunoradiometric assay had a sensitivity of 1.2 pg/ml (at 95% probability), and intra- and interassay coefficients of variation of 6.9–9.1% and 6.2–9.6% respectively. The cortisol assay had a sensitivity of 10 nmol/l, and intra- and interassay coefficients of variation of 2.8–5.1% and 5.3–9.2% respectively.

All patients underwent one desmopressin test 3–6 months postoperatively. After an overnight fast, an indwelling forearm cannula was inserted at 0830 h; the subject remained supine for the remainder of the test. At 0900 h, 10 μg desmopressin (Ferring, Gentilly, France) was injected intravenously as a bolus. Plasma ACTH and cortisol concentrations were measured at 0, 15, 30, 60, 90, 120 and 180 min after desmopressin administration. All patients were off hydrocortisone treatment 36–48 h before initiation of hormone evaluation.

Statistical analysis

Statistical analysis was analyzed by Mann-Whitney’s U test except for the differences between basal plasma ACTH and cortisol values and their secretion peaks after desmopressin injection which were analyzed using the Wilcoxon test and the sex ratio differences between groups using the \(\chi^2\) test. The Pearson’s correlation tests were performed on appropriate variables. Statistical significance was achieved at a \(P\) value less than 0.05. Determination of optimal thresholds for peak ACTH and cortisol values after desmopressin stimulation or for the percentage of variation of these values was performed using the receiver operator characteristic (ROC) curve method.
Results

Baseline and early postoperative data

We first compared baseline parameters in the R, IF and LR groups (Table 1). Age and sex ratio were not significantly different between outcome groups. Mean duration of follow-up was longer in the LR group than in the R group, only reflecting the higher rate of patients unavailable to long-term follow-up in the R group. As expected from the definition of each group (see Methods), early mean 24-h ACTH and cortisol plasma levels as well as UFC values were statistically different between the R and IF groups, while patients from the R and LR groups had statistically comparable values, as shown in Table 1.

Desmopressin test

Individual absolute plasma ACTH and cortisol values during the desmopressin test are presented in Fig. 1. As shown in Table 2, basal plasma ACTH before desmopressin injection was, as expected, significantly lower in the R group than in the IF group but was not different between the R group and the LR group. In absolute values, the ACTH peak after the desmopressin test was significantly higher in the LR group or IF group than in the R group as shown on Fig. 2. Importantly, although the initial features of the R and the LR groups were comparable (Table 1), peak values after desmopressin were significantly higher than baseline values in the LR group but not in the R group (Fig. 2). The percentage rise in ACTH plasma concentration after desmopressin injection was also statistically higher in the LR group or IF group than in the R group (Table 2).

Basal serum cortisol before desmopressin injection was significantly lower in the R group than in the IF group but was not different between the R group and the LR group. Serum cortisol peak after the desmopressin test was significantly lower in the R group than in the LR group or IF group (Table 2).

Unlike ACTH values, the percentage rise in cortisol serum concentration after desmopressin injection was not statistically different between the R and LR groups or between the R and IF groups (Table 2).

Predictive value for surgical failure

Using the ROC curve method, the threshold of positive stimulation after desmopressin injection was determined for each relevant parameter to try to best discriminate patients in remission (group R) from patients with later recurrence (group LR). These thresholds were the following: ACTH peak ≥ 22 pg/ml or ACTH rise ≥ 35%; cortisol peak ≥ 350 nmol/l or cortisol rise ≥ 14%. Performances of each individual threshold value are indicated in Table 3.

Using these criteria based on absolute values, none of the twelve patients in remission had both ACTH and cortisol values above these thresholds vs three of five patients from the LR group and five of five in the IF group. Symmetrically, ten of twelve of the patients in remission had both ACTH and cortisol values below these thresholds vs none of the patients from the LR or IF groups. Discrepant ACTH and cortisol responses were found in two of twelve patients in remission, and in two of five patients from the LR group.

Discussion

Cushing’s disease is a rare disease whose spontaneously fatal evolution calls for a radical treatment. Transsphenoidal microsurgery is the treatment of choice with an immediate remission rate of 69–94% according to some studies (1, 4–10). Immediate surgical failures are accounted for by partial tumor removal. The recurrence rate fluctuates between 4 and 32% in the literature for an average follow-up of 5 years. Part of this variability may be due to the fact that definition of remission criteria is highly variable. Most recurrences occur within 2 years after surgery, as was the case in four of five of our patients from the LR group, but some studies report recurrences more than 10 years postoperatively (1, 13, 14, 20). Such recurrences are likely due to regrowth of residual adenomatous tissue. Several potential factors have previously been studied to try to predict long-term surgical success or failure.

Table 1 Characteristics of the population and early postoperative data in 22 patients from the R, LR and IF groups. Values are means ± S.D.

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>LR</th>
<th>IF</th>
<th>R vs LR*</th>
<th>R vs IF*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33 ± 10</td>
<td>32 ± 12</td>
<td>44 ± 13</td>
<td>1</td>
<td>0.073</td>
<td></td>
</tr>
<tr>
<td>Sex ratio (F/M)</td>
<td>9/3</td>
<td>4/1</td>
<td>4/1</td>
<td>0.825</td>
<td>0.825</td>
<td></td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>3.5 ± 1.3</td>
<td>7.8 ± 3.6</td>
<td>3.9 ± 0.8</td>
<td>0.033</td>
<td>0.458</td>
<td></td>
</tr>
<tr>
<td>Mean plasma ACTH (pg/ml)</td>
<td>5 ± 5</td>
<td>10 ± 6</td>
<td>54 ± 18</td>
<td>0.138</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean plasma cortisol (nmol/l)</td>
<td>42 ± 33</td>
<td>40 ± 44</td>
<td>515 ± 165</td>
<td>0.673</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>UFC (nmol/day)</td>
<td>12 ± 26</td>
<td>8 ± 11</td>
<td>571 ± 334</td>
<td>0.647</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

* Mann–Whitney U test except for sex ratio ($\chi^2$ test).
Some parameters such as early postoperative cortisol levels (1, 16) or markers of tumor invasion (18) have been shown to provide a partial prediction of the likelihood of recurrence. For example, a serum cortisol value at 0900 h in excess of 100 nmol/l after pituitary surgery has been found to be associated with a higher risk of recurrence (16). Previous attempts at using dynamic tests in this setting, such as corticotropin-releasing hormone or ACTH tests, have provided controversial results (1, 19). In our experience, early postoperative cortisol measurements did not allow us to appropriately discriminate patients in long-term remission from those who will experience recurrence within 2–10 years (18). In our present series, early (7 days) postoperative cortisol values allowed us to identify all patients with immediate failure who had early postoperative cortisol values ranging from 291 to 731 nmol/l. However, one of twelve patients in

Table 2  Mean±s.d. basal and peak values and percentage ACTH and cortisol during the desmopressin test in 22 patients from the R, LR and IF groups.

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>LR</th>
<th>IF</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ACTH (pg/ml)</td>
<td>10±7</td>
<td>24±21</td>
<td>45±26</td>
<td>0.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Peak ACTH (pg/ml)</td>
<td>11±8</td>
<td>43±25</td>
<td>139±97</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>Basal cortisol (nmol/l)</td>
<td>111±132</td>
<td>249±134</td>
<td>536±121</td>
<td>0.028</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak cortisol (nmol/l)</td>
<td>147±166</td>
<td>478±231</td>
<td>822±390</td>
<td>0.013</td>
<td>0.003</td>
</tr>
<tr>
<td>% ACTH increment</td>
<td>26±64</td>
<td>129±137</td>
<td>205±129</td>
<td>0.035</td>
<td>0.008</td>
</tr>
<tr>
<td>% Cortisol increment</td>
<td>64±115</td>
<td>99±42</td>
<td>47±39</td>
<td>0.139</td>
<td>0.205</td>
</tr>
</tbody>
</table>

* Mann–Whitney U test.

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Figure 1  Individual basal and peak plasma (a) ACTH and (b) cortisol values during the desmopressin test in 22 patients after surgery for Cushing’s disease. Baseline values are indicated by open circles; solid circles denote peak values after i.v. injection of 10 μg desmopressin for each patient from the R, LR or IF groups. The threshold of positive stimulation as determined by ROC curve analysis is represented by the dotted lines.
long-term remission (61 months) had a mean cortisol 7
days after surgery above 100 nmol/l (107 nmol/l), and
in the five patients who had a later recurrence, early
postoperative cortisol was undetectable in two and
between 28 and 99 nmol/l in the other three. There-
fore, early postoperative cortisol did not allow an ade-
quately prediction of the long-term outcome of surgery
in our patients. In the present study, we have thus
shown the potential usefulness of a desmopressin test
in the postoperative follow-up of patients with Cush-
ing’s disease.

Previous studies have shown the potential interest of
the vasopressin (AVP) analog desmopressin in the diag-
osis of Cushing’s disease due to an overexpression of
the V1b/V3 subtype of the arginine vasopressin recep-
tor in adenomatous vs normal corticotroph cells (24,
33). Indeed, taking together the results from several
studies in a total of 192 subjects with Cushing’s dis-
ease, a positive cortisol response to desmopressin was
reported on average in 92% of patients, and an ACTH
response in 85% (17, 25, 26, 30, 31, 34). Definitions
for positive response may, however, differ slightly
between authors who also used different assays with
distinct characteristics. In the largest short-term pub-
lished series an ACTH increase of 30% and a cortisol
increase of 20% were considered as positive responses
(17). In the latter series, 50 of 87 patients tested pre-
and postoperatively showed disappearance of a positive
ACTH response to desmopressin after surgery, of whom
four were surgical failures, with a mean follow-up of 17
months (range, 2–54 months).

With a median follow-up of 4 years (minimum,
2 years; range, 24–141 months), we analyzed the
endocrine outcome of 22 operated patients, five of
whom could be classified into the IF group because of
a lack of biochemical cure: all of them indeed had elev-
ated 24-h plasma cortisol and UFC values at the first
postoperative evaluation. Among the 17 remaining
patients (median follow-up, 4 years; mean, 57
months), based on peak ACTH values, the postoperative
desmopressin test was predictive of a later recurrence
with a positive predictive value of 100% and a negative
predictive value of 92%. Indeed ACTH or cortisol peak
responses yielded the best predictive values when
expressed in absolute values.

A potential limitation of the use of this test is rep-
resented by the existence of false negative responses
in patients with Cushing’s disease: these were found
in 10–20% of patients (27, 28, 30). Furthermore, we
obviously cannot rule out that some of the patients cur-
rently classified as in remission will experience a later
recurrence, resulting in an underestimation of the posi-
tive predictive value of the test and overestimation of its
negative predictive value. This is made still more likely
by the fact that the mean duration of follow-up was sig-
ificantly longer in the LR group than in the R group.

When all of our patients were categorized into
each outcome group at 2 years of follow-up to control

Table 3 Performance characteristics of the desmopressin test as determined by ROC analysis in twelve patients in the R group and
five patients in the LR group.

<table>
<thead>
<tr>
<th>R vs LR</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive PV (%)</th>
<th>Negative PV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak ACTH ≥ 22 pg/ml</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>ACTH rise ≥ 35%</td>
<td>80</td>
<td>75</td>
<td>57</td>
<td>90</td>
</tr>
<tr>
<td>Peak cortisol ≥ 350 nmol/l</td>
<td>80</td>
<td>92</td>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td>Cortisol rise ≥ 14%</td>
<td>100</td>
<td>67</td>
<td>56</td>
<td>100</td>
</tr>
</tbody>
</table>

PV, predictive value.

Figure 2 Mean ± S.E.O basal (open bars) and peak (solid bars) plasma (a) ACTH (pg/ml) and (b) cortisol (nmol/l) during the desmopressin
test in twelve patients in the R group and in the five patients in the LR group. Statistical analysis was performed by Mann–Whitney’s U
test except for the differences between basal plasma ACTH and cortisol values and their secretion peaks which was performed using the
Wilcoxon test. * P < 0.05, ** P < 0.01, NS, not significant.
for a possible follow-up bias, only one patient who had been classified into the LR group because of a recurrence occurring 3 years after surgery fell into the R group: using the above-mentioned thresholds in absolute values, the sensitivity and specificity of the test as a predictive factor of recurrence would remain acceptable (75% and 92% respectively for ACTH and 75% and 85% respectively for cortisol).

In the present study reporting the long-term follow-up of patients after surgery for Cushing’s disease, desmopressin testing appeared as a potentially valuable tool to determine the likelihood of late recurrence of hypercortisolism. This test cannot, however, be recommended as a parameter of biological follow-up in patients who may have a false negative response to desmopressin preoperatively. In addition to previously validated parameters, mainly early postoperative cortisol levels, this test might help to define a subset of patients at higher risk of recurrence. The prognostic value of this test needs to be further validated by prospective studies.

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References


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