CLINICAL STUDY

Usefulness of the desmopressin test in the postoperative evaluation of patients with Cushing's disease

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Abstract

Objective: To evaluate the plasma ACTH and serum cortisol responses to desmopressin in patients with Cushing's disease either before or after pituitary adenomectomy during long-term follow-up, and to compare the results with those obtained after corticotrophin-releasing hormone (CRH) testing.

Design: Plasma ACTH and serum cortisol concentrations were evaluated after the administration of desmopressin (10 µg i.v.) or CRH (1 µg/kg i.v.) in 34 patients with Cushing's disease. Twenty-four patients with active Cushing's disease were evaluated both before and after transsphenoidal pituitary surgery (TSS); these patients were followed up for 1–36 months. Ten patients were studied only after a long-term period (1–19 years, median 4 years) after TSS (six patients), TSS plus external pituitary irradiation (three patients) and TSS plus radiosurgery (one patient).

Results: In 24 patients with active Cushing's disease a significant ACTH/cortisol response ($P < 0.001$) was induced by either desmopressin (ACTH from a baseline of 15.3 ± 2.7 pmol/l to a peak of 40.9 ± 7.3 pmol/l; cortisol from 673 ± 59 nmol/l to 1171 ± 90 nmol/l) or CRH (ACTH from a basal of 14.2 ± 2.5 pmol/l to a peak of 47.2 ± 7.7 pmol/l; cortisol from 672 ± 50 nmol/l to 1192 ± 80 nmol/l). In all patients a positive cortisol response to desmopressin was found. After pituitary adenomectomy the 14 'cured' patients were followed up for 1–36 months; desmopressin administration never induced ACTH or cortisol responsiveness in any patient. In contrast, a progressive recovery of ACTH and cortisol responses after CRH was observed at different intervals of time in all patients but one.

Five patients, in whom the cortisol concentration only normalized after surgery, showed a persistent responsiveness to desmopressin, and two of them relapsed 12 and 24 months later. In five patients who were not cured, the hormonal responsiveness to either CRH or desmopressin was similar before and after operation. Of 10 patients studied only after long-term follow-up, six were cured and a normal response to CRH was present, whereas no changes in ACTH/cortisol concentrations were induced by desmopressin. The other four unsuccessfully operated patients underwent pituitary irradiation and showed different and equivocal hormonal responses to desmopressin and to CRH.

Conclusions: During the postoperative follow-up of patients with Cushing's disease, the maintenance or the disappearance of the hormonal response may be related to the persistence or the complete removal of adenomatous corticotrophs, respectively. It is suggested that desmopressin test should be performed in the preoperative evaluation and follow-up of patients with ACTH-dependent Cushing's syndrome.

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Introduction

Corticotrophin-releasing hormone (CRH) has been used extensively for the differential diagnosis of Cushing's syndrome, causing significant ACTH/cortisol responses in most patients with Cushing's disease, but rarely in other forms of hypercortisolism (1).

Similar results have been obtained also with the synthetic analogue of vasopressin, lysine-vasopressin

(LVP) (2), through the action on V3 receptors recently cloned in the pituitary (3–5).

More recently, another synthetic vasopressin analogue, desmopressin, with more selective affinity for the renal V2 receptor but also able to interact with the V3 receptor, has been shown to induce significant increases in ACTH/cortisol in the majority of patients with Cushing's disease, but not in normal individuals (6–8). This latter finding might be of interest in clinical

Table 1 Some clinical characteristics of 34 patients with Cushing's disease, early postoperative results, and final outcome after follow-up.

Patient No.	Age (years)	Sex	Treatment	Cortisol concn after TSS† (nmol/l)	Subsequent treatment	Final outcome	Follow-up (months)
1	26	F	TSS	27	—	Cure	12, 24
2	28	F	TSS + TSS	49	—	Cure	12, 36
3	68	F	TSS	22	—	Cure	1, 6, 12, 24
4	33	F	TSS	27	—	Cure	1, 6, 12, 18, 24, 36
5	13	F	TSS	< 10	—	Cure	1
6	38	F	TSS	118	—	Cure	1, 6, 12, 18, 24, 36
7	34	F	TSS	37	—	Cure	1, 6, 12, 18, 24
8	31	F	TSS	100	—	Cure	1, 6, 12, 18, 24
9	70	F	TSS	107	—	Cure	1, 6, 12, 24
10	15	M	TSS	< 10	—	Cure	1, 6, 12, 18, 24
11	22	F	TSS	63	—	Cure	1, 6, 12
12	23	F	TSS	53	—	Cure	1, 6, 12
13	27	F	TSS	137	—	Cure	1, 6, 12, 18
14	31	F	TSS	34	—	Cure	1, 6, 12
15	47	F	TSS	545	—	Normalization	1, 6
16	17	F	TSS	201	—	Normalization	1, 6
17	42	F	TSS	605	—	Relapse	1, 12§
18	46	F	TSS	622	—	Normalization	1, 6, 18
19	29	F	TSS	408	—	Relapse	1, 6, 12, 18, 24
20	26	F	TSS	1109	γU + KC	Normalization	1
21	43	F	TSS	606	γU + KC	Normalization	1
22	23	F	TSS	814	KC	Normalization	1
23	37	F	TSS + TSS	740	ADRX	Hypoadrenalism‡	1
24	35	F	TSS	715	—	Failure	1§
25	34	F	TSS	109	—	Cure	84
26	41	F	TSS	104	—	Cure	231
27	33	M	TSS	66	—	Cure	48
28	39	F	TSS	27	—	Cure	60
29	25	F	TSS	< 10	—	Cure	36
30	28	F	TSS + TSS	< 10	—	Cure	24
31	45	F	TSS + TSS	726	RT	Cure	24, 36, 48
32	52	F	TSS	455	RT	Normalization	60, 72, 48
33	38	F	TSS	504	RT	Normalization	48, 72, 84
34	51	F	TSS	270	γU	Normalization	12, 24, 36

TSS, transsphenoidal surgery; γU, gamma unit; KC, ketoconazole; ADRX, bilateral adrenalectomy; RT, radiotherapy.

† Serum cortisol normal range = 140–700 nmol/l.

‡ After bilateral adrenalectomy; § lost to follow-up.

practice, as a certain degree of overlap occurs between hormonal responses in Cushing's disease and in normal individuals after administration of CRH and LVP.

The consistent lack of hormonal responses to desmopressin recorded in normal individuals might indicate the possible usefulness of this challenge in the post-surgical follow-up of Cushing's disease, for the recognition of true recurrences. In this respect, normal postoperative cortisol concentrations (9), hyperresponsiveness to CRH or metyrapone tests soon after surgery (10–12), or occasional paradoxical ACTH responses to the administration of thyrotrophin-releasing hormone (TRH)/gonadotrophin-releasing hormone (GnRH) (13, 14) have been associated with greater rates of relapse. Because, at present, no single test is considered to be of total value, the aim of the present study was to compare the ACTH/cortisol responses to desmopressin and CRH in patients with Cushing's disease either before or after pituitary adenomectomy during long-term follow-up.

Patients and methods

Patients

Thirty-four patients (32 women and 2 men, aged 13–70 years) were studied (Table 1). Twenty-four patients with active Cushing's disease were evaluated both before and after transsphenoidal pituitary surgery (TSS), and two of them also underwent stereotactic radiosurgery (Gamma Unit); these patients were followed up for 1–36 months.

Ten patients were studied only after a long-term period (1–19 years, median 4 years) after TSS (patients Nos 25–30), TSS plus external pituitary irradiation (total dose of 48–54 Gy, patients Nos 31–33) and TSS plus radiosurgery (patient No. 34). Four patients (Nos 2, 23, 30 and 31) were operated on twice.

The diagnosis of Cushing's disease was made on the basis of clinical features and standard hormonal criteria: high urinary free cortisol (UFC) excretion,

normal or high plasma ACTH and serum cortisol concentrations, absent suppression after low-dose dexamethasone tests (1 mg orally overnight and/or 2 mg/day orally for 48 h), but adequate suppression after high-dose dexamethasone tests (8 mg orally overnight and/or 8 mg/day orally for 48 h). Nuclear magnetic resonance imaging (MRI) and/or high resolution computed tomography of the sellar region showed a pituitary microadenoma in all but three patients (Nos 6, 14 and 26); two patients (Nos 20 and 32) had a macroadenoma. The diagnosis of Cushing's disease was confirmed in all patients after pituitary adenectomy, as the histological examination showed the existence of adenomatous tissue, with positive staining for ACTH at immunohistochemical analysis.

Ten normal individuals (four women and six men, aged 23–31 years), recruited from medical staff, served as controls for the desmopressin test.

Testing procedures

All patients gave informed consent and underwent desmopressin and CRH tests in randomized order, starting at 0800 h after an overnight fast.

Desmopressin (Minirin/DDAVP, Ferring-S, Milan, Italy) was injected at a dose of 10 µg i.v. as a bolus at time 0 min and blood samples for plasma ACTH and serum cortisol determinations were taken at –30, 0, 15, 30, 45, 60, 90 and 120 min.

Ovine CRH (Cinalfa, Läufelfingen, Switzerland) was administered at the dose of 1 µg/kg i.v. as a bolus at time 0 min, with blood samples taken at –30, 0, 20, 30, 60, 90 and 120 min.

In 24 patients, desmopressin and CRH tests were performed either before or after pituitary surgery. Fourteen (Nos 1–14) of them were judged as 'cured' on the basis of hormonal and clinical criteria. Serum cortisol concentrations were less than 140 nmol/l 2–7 days after surgery; 30 days after TSS, UFC values were less than 35 nmol/day and a normal cortisol suppression was present after 1 mg dexamethasone (i.e. cortisol concentrations less than 140 nmol/l). All patients needed corticosteroid replacement therapy (cortisone acetate 25–37.5 mg/day). The dose was tapered and treatment stopped at least 24 h before the patients were investigated during the post-surgical follow-up (at 1, 6, 12, 18, 24 and 36 months). The replacement therapy was completely withdrawn on the basis of clinical criteria and when baseline cortisol/ACTH concentrations normalized and hypothalamic–pituitary–adrenal function fully recovered.

Five patients (Nos 15–19) only achieved normal cortisol concentrations (ranging between 140 and 700 nmol/l) 2–7 days after adenectomy. At the first month after TSS, UFC values were within the normal range (35–275 nmol/day) and serum cortisol was suppressed by 1 mg dexamethasone. In these patients,

desmopressin and CRH challenges were repeated at 1, 6, 12, 18 and 24 months.

Five patients (Nos 20–24) who were operated on unsuccessfully underwent desmopressin and CRH tests only at 1 month after surgery.

Six of the remaining 10 patients (Nos 25–30) were cured and were investigated in conditions of persistent eucortisolism at 27–231 months after TSS; the other four patients not cured by surgery improved after pituitary irradiation and underwent both tests on repeated occasions (range 12–84 months).

Hormone measurements

Plasma ACTH (1 pmol/l = 4.5 pg/ml) and serum cortisol (1 nmol/l = 0.0362 µg/dl) concentrations were measured on unextracted samples by IRMA (Nichols Institute, San Juan Capistrano, CA, USA) and RIA (Diagnostic Products, Los Angeles, CA, USA) methods, respectively. The intra- and interassay coefficients of variation were 3.1–7.3% and 4.6–5.4%, respectively. The lower limits of sensitivity were 0.44 pmol/l for plasma ACTH and 11 nmol/l for serum cortisol.

Statistical analysis

As previously defined (8), in each patient increases in ACTH and cortisol greater than 50% and 20% from baseline values, respectively (mean value of samples taken at –30 and 0 min) were considered as positive responses to both tests. When net increments (Δ) in ACTH and cortisol were respectively less than 5 pmol/l and 200 nmol/l, the hormonal response was considered insufficient, irrespective of the percentage increase.

Statistical analysis was performed by Student's *t*-test and by ANOVA test followed by Scheffé *F*-test.

Results

Normal individuals

Desmopressin administration did not elicit significant ACTH or cortisol responses in any normal individuals (ACTH from a baseline of 5.1 ± 1.2 pmol/l to a peak of 5.5 ± 0.9 pmol/l; cortisol from 404 ± 33 nmol/l to 420 ± 48 nmol/l; Fig. 1); the net increments ranged from –2 to 3.3 pmol/l for ACTH and from –48 to 150 nmol/l for cortisol.

Patients with Cushing's disease: before surgery

In 24 patients (Nos 1–24) with active Cushing's disease, a significant ACTH/cortisol response ($P < 0.001$) was induced by either desmopressin (ACTH from a baseline of 15.3 ± 2.7 pmol/l to a peak of 40.9 ± 7.3 pmol/l; cortisol from 673 ± 59 nmol/l to 1171 ± 90 nmol/l; Fig. 1) or CRH (ACTH from a basal of 14.2 ± 2.5 pmol/l to a peak of 47.2 ± 7.7 pmol/l; cortisol from 672 ± 50 nmol/l to

Figure 1 Changes in plasma ACTH and serum cortisol concentrations (means $\pm$ s.e.) after 10 μ g i.v. desmopressin in 24 patients with active Cushing's disease (Nos 1–24, ▲), in 12 'cured' patients 1 month after surgery (Nos 3–14, ◊), in five unsuccessfully operated (Nos 20–24, △), in five 'normalized' patients (Nos 15–19, ○) and in 10 normal subjects (□, dotted lines). Positive responses were observed in patients with active Cushing's disease, in unsuccessfully operated and in 'normalized' patients.

1192 $\pm$ 80 nmol/l). In all patients a positive cortisol response to desmopressin was found, but four patients (Nos 1, 7, 13 and 16) did not show a significant increase in ACTH after desmopressin. An absent ACTH and cortisol response after CRH administration was observed only in one woman (patient No. 6).

Patients with Cushing's disease: follow-up after surgery alone or surgery plus radiotherapy

The 14 'cured' patients (Nos 1–14) were followed up for 1–36 months after pituitary adenectomy. One

Figure 2 Absence of increase in serum cortisol (means $\pm$ s.e.) after 10 μ g i.v. desmopressin in 'cured' patients at 1 month after surgery ($n=12$, ■), 6 months ($n=11$, □), 12 months ($n=13$, ●), 18 months ($n=6$, ○), 24 months ($n=8$, ▲), and 36 months after surgery ($n=3$, △).

month after surgery, neither ACTH nor cortisol responses were observed after desmopressin (Fig. 1); no different hormonal responsiveness was found between the four patients with low-normal cortisol concentrations (Nos 6, 8, 9 and 13) and the remaining 10 patients (data not shown). During the follow-up period, in spite of a progressive increase in baseline cortisol concentrations from the 1st to the 36th month, desmopressin administration never induced a positive increase in cortisol in any patient (Fig. 2). In contrast, a progressive recovery of ACTH and cortisol responses after CRH was observed at different intervals of time in all patients but one (No. 8). Figure 3 shows the pattern of cortisol responses to desmopressin and CRH during follow-up. One month after surgery, the CRH test induced a positive increase in ACTH in three of 12 patients (Nos 5, 11 and 14), but no cortisol responses were recorded. At the 6th month, normal ACTH and cortisol responses to CRH were observed in four of 11 patients (Nos 6, 7, 12 and 14). Twelve months after surgery, nine of 13 patients (Nos 1, 2, 6, 7, 9, 10, 11, 12 and 14) showed an increase in ACTH after CRH and seven (Nos 2, 6, 7, 9, 12, 13 and 14) showed a normal cortisol increment. At the 18th month, positive ACTH and cortisol responses after CRH were observed in four of six cases (Nos 6, 7, 10 and 13). Two years after adenectomy, five of the eight investigated patients (Nos 1, 4, 6, 7 and 10) showed a normal increase in ACTH/cortisol after CRH, and two (Nos 3 and 9) exhibited only a cortisol response. At the 36th month, only three patients were evaluated (Nos 2, 4 and 6), and they showed a positive responsiveness to CRH.

Figure 3 Net increments (Δ) in serum cortisol after desmopressin and CRH in 14 cured patients (○, non-responders; ●, responders) with Cushing's disease, at 1, 6, 12, 18, 24 and 36 months after pituitary adenectomy. A persistent absent response to desmopressin is shown, but a progressive recovery of responsiveness to CRH is observed. The horizontal dotted lines indicate the lower limits of positive responses.

Five patients (Nos 15–19) who only achieved normal cortisol concentrations soon after surgery, were followed up (Fig. 4). One month after operation, the ACTH and cortisol response curves after desmopressin were significantly different from those in normal individuals ($P < 0.05$) and did not differ from those of patients who were not cured (Fig. 1). Notably, at the 1st month three patients (Nos 15, 17 and 18) showed positive ACTH and cortisol responses to desmopressin, whereas in one patient (No. 16) desmopressin induced only an increase in cortisol, as in her preoperative evaluation; these four patients were CRH responders, also. During the follow-up, this pattern of responsiveness was maintained at the 6th (patients Nos 15, 16 and 18), 12th (patient No. 17) and 18th months (patient No. 18). It should be noted that, in patient No. 17, UFC excretion increased after

the 6th month, whereas a normal cortisol inhibition was maintained; at the 12 month a clinical relapse and a positive visualization of adenoma appeared at MRI. In patient No. 19, a positive increase in cortisol after desmopressin was present from 1–24 months, whereas serum cortisol responded to CRH and was not suppressed by dexamethasone only after the 18th month. A clinical recurrence with high UFC values and positive MRI (which had been negative at the 12th month) appeared at the 24th month. Five patients (Nos 20–24) underwent unsuccessful surgery: their hormonal responsiveness to either CRH or desmopressin (Fig. 1) was superimposable before and after operation.

Ten patients (Nos 25–34) were studied only after long-term follow-up. Six of them were cured (Nos 25–30) and a normal responsiveness to CRH was present, whereas no changes in ACTH and cortisol concentrations were induced by desmopressin. The other four patients (Nos 31–34) had been operated on unsuccessfully and then underwent pituitary irradiation. One of them (No. 31) showed a persistent hormonal response to desmopressin 24 months after irradiation (Δ ACTH 7.9 pmol/l; Δ cortisol 452 nmol/l); subsequently, the response to desmopressin was reduced, a hypocortisolism occurred and cortisone substitutive therapy was started. In patients Nos 32 and 33, desmopressin persistently increased ACTH concentrations (No. 32: Δ ACTH 5.7–14.1 pmol/l; No. 33: Δ ACTH 9.9–18.5 pmol/l), whereas it induced either insufficient or positive increases in cortisol (No. 32: Δ cortisol 114–239 nmol/l; No. 33: Δ cortisol 34–264 nmol/l); the same pattern of equivocal responsiveness was also recorded after CRH testing. Patient No. 34 did not respond to desmopressin 12 months after radiosurgery, but positive increments reappeared at 24 and 36 months of follow-up (24th month: Δ ACTH 7.4 pmol/l, Δ cortisol 185 nmol/l; 36th month: Δ ACTH 12.5 pmol/l, Δ cortisol 889 nmol/l); throughout this period an ACTH/cortisol response to CRH test had been always present.

Discussion

Long-standing experience with the CRH test has shown that this peptide is able to induce a significant increase in plasma ACTH and serum cortisol in the great majority of patients with Cushing's disease, whereas this pattern of response rarely occurs in other forms of hypercortisolism (1). Moreover, the ACTH-releasing activity of vasopressin and its analogues, mediated by the V3 (V1b) receptors recently cloned in the pituitary (3, 4), has led to the use of desmopressin in trying to discriminate better between pituitary or ectopic sources of ACTH hypersecretion in ACTH-dependent Cushing's syndrome. With a greater relative affinity for the renal V2 receptors and less action on V1 pressor receptor family, desmopressin has replaced arginine- and lysine-vasopressin in clinical testing for Cushing's syndrome,

Figure 4 Net increments (Δ) in serum cortisol after desmopressin (desm, open symbols) and CRH (closed symbols) in the five patients who had normal postoperative cortisol concentrations, at 1, 6, 12, 18 and 24 months after surgery. The horizontal dotted lines indicate the lower limits of positive responses. The asterisks indicate the appearance of relapse in patients Nos 17 and 19.

thanks to the virtual absence of side-effects. Presumably because of overexpression of V3 receptors and/or expression of V2 receptors in corticotrophinomas (5), experience accumulated up to now has documented that, similarly to administration of CRH, that of desmopressin causes significant increases in ACTH and cortisol in most patients with Cushing's disease (6–8, 15). However, evidence that the same pattern of response occurs in some patients with ectopic Cushing's syndrome has been presented in either published (7, 16) or preliminary reports (17–19), and in this context the expression of both V3 and V2 vasopressin receptor subtypes in bronchial carcinoids has been demonstrated (5, 16, 20). At present, it appears that the value of the desmopressin test in the differential diagnosis of ACTH-dependent Cushing's syndrome is questionable, although in individual patients it may represent an adjunctive tool, particularly in cases of doubtful hormonal results after CRH or other dynamic tests. Indeed, improved discrimination between Cushing's disease and ectopic Cushing's syndrome was achieved with a combined test with both desmopressin and CRH injection (7).

The results here reported extend, therefore, those in our previous paper (8), particularly with respect to the possible clinical value of the desmopressin test during the post-surgical follow-up of Cushing's disease.

Notwithstanding the aforementioned remarks concerning the 'doubtful' diagnostic usefulness of desmopressin test, our data do confirm that, given a significant increase in ACTH and/or cortisol after desmopressin in an individual patient with Cushing's disease, the same pattern of response is reproducible in cases of unsuccessful surgery, as occurred in five of our patients studied before and after operation. In line with this, and even in the absence of data concerning the desmopressin test before pituitary adenomectomy, the finding of persistent ACTH responses to this peptide in another

three unsuccessfully operated and subsequently irradiated patients (Nos 32–34) may suggest the persistence of adenomatous corticotrophs after long-term follow-up.

In another two patients (Nos 17 and 19) who only achieved normal cortisol concentrations soon after surgery, a clinical and biochemical recurrence of Cushing's disease occurred after 12 and 24 months, respectively. Interestingly, whereas the hormonal response to desmopressin in both patients had reappeared at the 1st month and never disappeared during follow-up, in one of them the initially absent cortisol response to CRH – and the lack of suppressibility by dexamethasone – reappeared only after 18 months. Although a clinical recurrence of the disease occurred only months later, it is difficult to speak in terms of 'true recurrence' in these patients, as the finding of normal cortisol concentrations in the immediate post-surgical period has been related to an incomplete removal of adenomatous corticotrophs. Therefore, the persistent responsiveness to desmopressin may be a constant feature of unsuccessful surgery, even in the absence of clinical and biochemical evidence of active Cushing's disease. It is suggested that these patients need a more strict follow-up, with a monthly hormonal evaluation; if the hypercortisolism is confirmed and clinical features also appear, further therapeutic intervention is required.

Compared with our previous results (8), the data obtained in a larger group of normal individuals confirm the consistent lack of significant ACTH/cortisol responses to this peptide in this population (6, 15, 21) – a feature that might be a consequence of an insufficient expression of V3 receptors in normal corticotrophs. This consideration prompted us to evaluate whether the desmopressin challenge might be of value in the postoperative follow-up of patients with Cushing's disease after successful surgery.

Although it is generally accepted that the finding of low serum and urinary cortisol concentrations soon after adenomectomy provides the best predictive index of 'cure' of the disease (9, 10, 14), the overall data concerning the long-term follow-up of large series of patients indicate that a risk of 'true recurrences' is always present. It has been suggested that the finding of ACTH hyperresponsiveness to an early postoperative CRH test might be a valuable index with which to identify those patients with a greater risk of recurrence (10, 22) and this criterion was judged to be more specific than the demonstration of subnormal serum and urinary cortisol values soon after surgery (11). Moreover, the occurrence of preoperative paradoxical responses to TRH/GnRH has also been related to a greater percentage of relapse, although in very few patients (13, 14), and it has been recently shown that the metyrapone test is useful for the early detection of patients at risk of a recurrence (12). However, no single test exists that provides an accurate prediction of relapse of hypercortisolism, and problems can arise in the correct and early recognition of this situation, particularly during the recovery of 'normal' hypothalamic-pituitary-adrenal function. In this regard, the CRH test is no exception; our results in 14 patients exhibiting hypocortisolism immediately after surgery reflected the common experience with this peptide. In fact, a progressive recovery of positive ACTH/cortisol responses occurred in 13 of them, particularly after the 6th month, concomitant with the withdrawal of replacement therapy and, notably, with a substantial overlap compared with responses obtained before surgery. Different conclusions can be drawn from the results of the desmopressin test in the same patients, as the positive responsiveness recorded during active disease disappeared completely after surgery, and remained unchanged throughout the entire period of follow-up. In addition, an absent hormonal response was observed in another six patients studied only after operation and who remain persistently cured after 2–19 years of follow-up; it is of interest that a lack of responsiveness was found 4–19 years after surgery also in three patients (Nos 25–27) with low-normal cortisol concentrations in the early postoperative period. These findings confirm the complementary role of the desmopressin challenge with respect to the CRH test in the follow-up of Cushing's disease, as the disappearance of hormonal responses to this peptide seems to be a constant feature of patients who had been cured by either surgical or radiation therapy. In this context, desmopressin might provide improved discrimination of cure, as it seems helpful in better recognizing whether the recovery of ACTH/cortisol responses to CRH represents a recovery of normal pituitary-adrenal function or, instead, a reactivation of the disease. However, the present data need to be confirmed with longer periods of follow-up and wider experience with this test.

In conclusion, apart from diagnostic purposes, a positive ACTH/cortisol response to desmopressin in Cushing's patients retains value as an individual marker of the disease. Moreover, during the follow-up, the maintenance or disappearance of the hormonal response may be related to the persistence or complete removal of adenomatous corticotrophs, respectively. As release of ACTH and cortisol after desmopressin occurs in most patients with ACTH-secreting pituitary adenomas, it is mandatory to perform the test as part of the preoperative investigation, in order to interpret its results during the follow-up. Further studies are needed to determine whether this test may become a useful adjunct in detecting the risk of a 'true' recurrence of disease in patients with postoperative hypoadrenalism and who do not respond to the peptide after 'cure'.

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