CLINICAL STUDY

Desmopressin test during petrosal sinus sampling: a valuable tool to discriminate pituitary or ectopic ACTH-dependent Cushing's syndrome

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Abstract

Corticotropin-releasing hormone (CRH)-stimulated petrosal sinus sampling is currently the gold standard method for the differential diagnosis between pituitary and ectopic ACTH-dependent Cushing's syndrome. Our objective was to determine sensitivity and specificity of desmopressin test during petrosal sinus sampling.

Patients and methods: Forty-three patients had petrosal sinus sampling because of the lack of visible adenoma on magnetic resonance imaging (MRI) and/or because of discordant cortisol response to high-dose dexamethasone suppression test. ACTH sampling was performed in an antecubital vein, right and left petrosal sinuses, then at each location 5 and 10 min after injection of desmopressin. Diagnosis was based on the ACTH ratio between petrosal sinus and humeral vein ACTH after desmopressin test. Diagnosis was confirmed after surgery. A receiver operating characteristics curve was used to determine optimal sensitivity and specificity.

Results: Thirty-six patients had Cushing's disease (CD) and seven had ectopic ACTH secretion. A ratio > 2 after desmopressin was found in 35 of the 36 cases of CD (sensitivity: 95%). A ratio ≤ 2 was found in the seven patients with ectopic ACTH secretion (specificity: 100%). Sinus sampling was ineffective in determining the left or right localization of the adenoma (sensitivity = 50%). No major adverse effects were observed during or after the procedure.

Conclusion: Desmopressin test during petrosal sinus sampling is a safe and effective diagnostic procedure in ACTH-dependent Cushing's syndrome. It thus represents a valuable alternative to CRH.

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Introduction

Adrenocorticotropin (ACTH)-dependent Cushing's syndrome may be caused by a pituitary corticotrope adenoma (Cushing's disease (CD), 80–85% of cases), by an extrapituitary tumor (ectopic ACTH secretion (EAS)), or very rarely by a corticotropin-releasing hormone (CRH)-secreting tumor (ectopic CRH syndrome). When diagnosed, because of signs and symptoms of chronic endogenous glucocorticoid excess, most corticotrope adenomas are microadenomas (< 10 mm in largest diameter) (1, 2). Distinguishing between CD and EAS can be difficult because clinical and biological features are often similar, the source of ACTH secretion is not always readily identified by pituitary magnetic resonance (MR) imaging in case of small microadenomas, or by current imaging techniques in case of ectopic source. Moreover, classical diagnostic tests are sometimes discordant: for instance, partial suppression of cortisol after high-dose dexamethasone test (3–5).

Simultaneous bilateral inferior petrosal sinus catheterization and sampling, with CRH stimulation, is currently the gold standard to differentiate between CD and EAS. This procedure has been initially reported to have 100% sensitivity and specificity (6). However, since the first published series in the early 1990s, other reports have shown the technique to have much less discriminatory power (7–12).

Among the various agents that may interfere with the complex regulation of the hypothalamus–pituitary–adrenal axis, vasopressin is one of the most powerful stimuli of ACTH secretion via its binding to pituitary vasopressin type 3 (V3) receptors (13, 14). Desmopressin, a vasopressin agonist, could indeed theoretically stimulate adrenocorticotropin secretion by a pituitary tumor that expresses V2 and V3 receptors. However, few researchers observed the expression of V2 and V3 receptors in some ectopic tumors producing ACTH (15, 16).

Since 1995, we substituted CRH by desmopressin in bilateral inferior petrosal sinus sampling (IPSS).

The aim of our study was to evaluate this procedure as a diagnostic tool in the diagnosis of CD and EAS. We assessed the efficacy of this technique in 43 patients and defined a cut-off value for highest sensitivity and specificity. In this setting, the desmopressin test during the IPSS appeared as a safe and consistent procedure.

Patients and methods

Patients

Between 1995 and 2005, bilateral IPSS was performed in 36 patients because of clinical and biological evidence of ACTH-dependent Cushing's syndrome without MR image of the adenoma (80%) or because of discordant cortisol response to high-dose dexamethasone suppression test (20%); in seven of them because of lack of MR image and of cortisol suppression. We retrospectively evaluated these cases to determine (1) whether sampling was useful in differentiating CD and EAS and (2) in case of CD, whether it could be helpful for the neurosurgeon in determining the left or right lateralization of the adenoma.

The diagnosis of CD ($n=36$) was confirmed by histological examination of a surgical specimen in 28 patients, or on the basis of long-term remission after surgical treatment despite the lack of available tumor fragments for histological examination (five patients), or in case of remission after pituitary radiosurgery (three patients). The diagnosis of ACTH ectopic secretion was proven by histological examination of the specimen in seven cases (four patients with bronchial carcinoid, one with pancreatic carcinoma, one with thymic carcinoid and one with medullar carcinoma of the thyroid). Diagnoses were established in 43 patients with hypercortisolism who underwent successful sampling, i.e. 36 patients with CD and 7 with EAS.

The predictive value of simultaneous bilateral sampling of the inferior petrosal sinuses for determining the lateralization of the microadenoma was assessed in the 28 patients in whom microadenoma was identified intraoperatively as being either on one side or at the midline of the pituitary.

Catheterization procedure

Catheterization of both inferior petrosal sinuses was performed through a percutaneous bilateral femoral vein approach. After a catheter was advanced into a petrosal sinus, a small amount of contrast material was injected to verify the location of the catheter tip. Blood was slowly withdrawn from both catheters simultaneously and from a peripheral vein for adrenocorticotropin measurement. Desmopressin in a dose of 10 μ g was then infused into a peripheral vein, and samples were simultaneously obtained from both inferior petrosal sinuses and peripheral vein 5 and 10 min

after the administration of desmopressin. No anticoagulation was used during the procedure.

For the differential diagnosis between CD and EAS, the ACTH values were used to calculate the ratio of ACTH between the right or left inferior petrosal sinus and the concentration in the peripheral blood (IPS:P ratio) and the maximal ratio (right or left) was identified. Sampling giving the highest value of ACTH (5 or 10 min after the injection of desmopressin) was used to determine the ratio. The ratio corresponding to the highest sensitivity and specificity was determined using a receiver operator characteristics (ROC) curve.

To correlate the results of sampling with the site of the microadenoma in the pituitary gland, the location of the microadenoma as identified at surgery was assigned to the right or left side of the pituitary. The concurrent ACTH concentration in the inferior petrosal sinuses was used to calculate a ratio between the concentration of the two sides (lateralization gradient, L ratio).

Statistical analysis

Data were analyzed using non-parametric tests, using Microsoft Office Excel and SPSS (version 13.0 for Windows; SPSS Inc., Chicago, IL, USA). The Wilcoxon test was used for the analysis of the variations of plasma ACTH before and after desmopressin stimulation, P was considered significant when <0.05 . Sensitivity and specificity were derived from the ROC curve.

Results

Sampling was successfully performed in all of our patients ($n=43$). Bilateral catheterization was possible in all but one, in whom positioning of catheter in the left sinus was impossible due to congenital malformation (only one jugular vein was present). Indeed, each inferior petrosal sinus and humeral vein were simultaneously sampled in 42 patients. Individual data with the results of high-dose dexamethasone suppression test, MRI, petrosal sinus sampling, and surgically proven diagnosis are given in Table 1. Results between high-dose dexamethasone suppression test and IPSS were discordant in 20% of cases. Mean and extreme values of ACTH sampling before and after stimulation in each etiologic group of patients (CD or EAS) are given in Table 2.

IPS:P ratio in basal sampling

The ratio value corresponding to the highest sensitivity and specificity for differential diagnosis between CD and EAS was defined with a ROC curve: the defined optimal cut-off value of 2 was used for statistical analysis (Fig. 1). Out of the 36 patients with CD, 32 had an ACTH IPS:P ratio >2 (sensitivity 86%). Out of the seven patients with EAS, six had a maximal basal IPS:P ratio

Table 1 Individual data in 43 patients, with the results of high-dose dexamethasone suppression test, magnetic resonance (MR) imaging (either presence or lack of clearly visible image of pituitary adenoma), central-to-periphery adrenocorticotropin (ACTH) gradient in favor of Cushing's disease, and diagnosis as confirmed after surgery.

Patient number	Sex/age	HDDT cortisol suppression	Evident MR image	IPSS gradient >2	Surgical diagnosis
1	M/31	No	Yes	Yes	CD
2	F/60	No	Yes	Yes	CD
3	F/14	No	Yes	Yes	CD
4	F/73	No	Yes	Yes	CD
5	F/53	No	Yes	Yes	CD
6	F/42	No	Yes	Yes	CD
7	M/32	No	Yes	Yes	CD
8	M/50	Yes	No	No	CD
9	F/20	Yes	No	Yes	CD
10	F/56	Yes	No	Yes	CD
11	F/42	Yes	No	Yes	CD
12	F/50	Yes	No	Yes	CD
13	F/8	Yes	No	Yes	CD
14	F/48	Yes	No	Yes	CD
15	F/31	Yes	No	Yes	CD
16	F/50	Yes	No	Yes	CD
17	F/72	Yes	No	Yes	CD
18	F/46	Yes	No	Yes	CD
19	F/17	Yes	No	Yes	CD
20	F/50	Yes	No	Yes	CD
21	F/53	Yes	No	Yes	CD
22	F/46	Yes	No	Yes	CD
23	F/55	Yes	No	Yes	CD
24	M/36	Yes	No	Yes	CD
25	F/58	Yes	No	Yes	CD
26	F/26	Yes	No	Yes	CD
27	M/53	Yes	No	Yes	CD
28	F/28	Yes	No	Yes	CD
29	F/42	Yes	No	Yes	CD
30	M/45	Yes	No	Yes	CD
31	F/32	Yes	No	Yes	CD
32	M/38	Yes	No	Yes	CD
33	F/39	yes	No	Yes	CD
34	F/45	Yes	No	Yes	CD
35	F/24	Yes	No	Yes	CD
36	F/24	Yes	No	Yes	CD
37	M/61	No	No	No	EAS
38	F/50	No	No	No	EAS
39	F/63	No	No	No	EAS
40	M/58	No	No	No	EAS
41	F/69	No	No	No	EAS
42	F/39	No	No	No	EAS
43	F/59	No	No	No	EAS

F, female; M, male; HDDT, high-dose dexamethasone test; CD, Cushing's disease; and EAS, ectopic adrenocorticotropin secretion. As detailed in text, only one patient (#8, bold) with CD had an IPSS gradient <2.

of <2. Thus, the diagnostic specificity of a basal ratio >2 was 85%.

IPS:P ratio after desmopressin stimulation

Out of the 36 patients with CD, 32 had an ACTH ratio >2 (sensitivity 97%) (Fig. 2). The only case where we observed falsely negative results was a male aged 50, who presented typical clinical hypercortisolism with normal pituitary MR imaging; highest basal ratio was 1.09, increasing to 1.16 after desmopressin; explorative transsphenoidal surgery, finally performed because of the lack of consistent findings supporting an ectopic secretion, found a microadenoma of

the left side of the pituitary, confirmed by histological examination, measuring 1 mm at its largest diameter. All of the seven patients with EAS had a maximal basal IPS:P ratio of <2.0 (specificity 100%) (Table 2).

Ratio increased from 11.6 to 27.8 after desmopressin for patients with CD ($P<0.05$), and remained unchanged (1.7 vs 1.33, $P<0.05$) in patients with EAS.

Lateralization of the microadenoma in CD

Pituitary adenoma was surgically confirmed in 28 cases. Fifteen patients (54%) had an intersinus gradient

Table 2 Values of adrenocorticotropin (ACTH; pg/ml) before and after desmopressin stimulation in periphery (humeral vein) and in each petrosal sinus.

	Cushing's disease (n=36)	Ectopic ACTH secretion (n=7)
Basal ACTH		
Humeral	55 (5–255)	97.25 (12–205)
Right IPS	436 (25–2120)*	112.5 (17–238)
Left IPS	188 (5–800)	118.25 (40–240)
Maximal post-stimulation ACTH		
Humeral	216 (22–1840)	146 (16–195)
Right IPS	3058 (63–38 900)*	166 (18–205)
Left IPS	2118 (24–26 600)*	158 (32–221)
Basal IPS:P ratio	11.6 (1.1–64.8)*	1.7 (1.09–3.33)
Maximal post-stimulation IPS:P ratio	27.8 (1.16–474.4)*	1.33 (1.13–1.90)

Values of the ratio between petrosal sinus and humeral ACTH sampling before and after desmopressin stimulation. *Denotes a significant difference between Cushing's disease and ectopic adrenocorticotropin secretion ($P<0.05$). IPS, inferior petrosal sinus; P, periphery (humeral vein).

corresponding to the left or right side of the adenoma. This result was not modified after injection of desmopressin. The wide range of results in the lateralization ratio (L ratio; ranging from 1 to 35 when wrong side was indicated, and 1.1 to 14 when correct side was indicated), even after stimulation, made it impossible to determine a correct maximal value of L ratio that would be indicative of the exact lateralization.

Complications

In seven patients, catheterization led to hematomas at the site of venous puncture. No major complication was observed.

Figure 1 Receiver operator characteristics curve. Value of the ACTH ratio between intrapetrosal and humeral sampling after desmopressin stimulation. Insert: sensitivity and specificity according to the ratio between petrosal sinus and humeral ACTH sampling after desmopressin stimulation. Highest sensitivity and specificity were obtained with a ratio cut-off value of 2.

Discussion

Both low- and high-dose dexamethasone suppression tests have been widely used for the differential diagnosis between EAS and CD. However, even combined with CRH stimulation test, these tests do not give optimal

Figure 2 Ratio between intrapetrosal and periphery ACTH sampling (IPS:P ratio) in 43 patients, with Cushing's disease ($n=36$) or ectopic adrenocorticotropin secretion ($n=7$). Ratio after desmopressin stimulation is represented on a logarithmic scale.

Table 3 Performance (specificity and sensitivity) of the desmopressin test during inferior petrosal sinus sampling (IPSS) alone or coupled with corticotropin-releasing hormone (CRH), in the present study and published reports.

Author	Procedure	Patients with CD	Patients with EAS	Sensitivity	Specificity
Our study	Desmopressin	36	7	0.97	1
Machado <i>et al.</i> (26)	Desmopressin	50	5	0.92	1
Tsagarakis <i>et al.</i> (33)	CRH and desmopressin	47	7	0.97	1

Number of patients (*n*) described with Cushing's disease (CD) or ectopic ACTH secretion (EAS).

sensitivity and specificity (2). The use of the inferior petrosal sinus catheterization procedure was first described by Corrigan in 1977 in the differential diagnosis between both conditions (17). This diagnostic procedure was improved by the addition of CRH stimulation described by Landolt *et al.* in 1986 (18).

The first large-scale study published by Oldfield in 1991 on CRH-stimulated bilateral IPSS reported an accuracy of 100%, but as many as 15% of the patients had an uncertain diagnosis, making it difficult to assess actual performance of the procedure (6). Several studies were then published with the use of CRH, showing a wide range of accuracy rates varying from 80 to 100% (19–24). Our study, based on desmopressin-stimulated IPSS, found comparable results with a sensitivity of 96% and a specificity of 100% with a similar cut-off value of 2 determined by ROC curve analysis.

Two series have been published previously with the use of desmopressin-stimulated intrapetrosal sinus sampling. The first (*n*=26 patients with CD and 4 with EAS) tried to compare the use of CRH with desmopressin during bilateral petrosal sinus sampling – the procedure showed an accuracy of about 90% of cases in differentiating CD and ectopic ACTH secretion (25). The second (*n*=56 patients, 5 EAS) found a sensitivity of 92% and a specificity of 100% (26). In both studies, stimulation by desmopressin allowed an increase in sensitivity from 80 to more than 90%. The central-to-periphery ratio cut-off value of 2 was determined in our series by ROC curve to differentiate CD (ratio > 2) and EAS (ratio ≤ 2). The same value was used in the largest series based on desmopressin-stimulated petrosal sinus sampling (26). A central to periphery ratio value of 3 was classically used in the series using CRH stimulation (6).

The rationale for the use of desmopressin, a long-acting synthetic vasopressin analog, in the diagnosis of CD, is based on the overexpression of V2 desmopressin receptors in corticotrope adenoma cells (27). The injection of desmopressin stimulates the secretion of ACTH in case of CD, and theoretically not in EAS (28). However, a few studies described occasional expression of desmopressin receptors in ectopic adrenocorticotropin secretion (15, 16, 29, 30). Our study found a clear difference between both conditions after stimulation by desmopressin, with a significantly increased gradient in case of CD and not in EAS.

As expected, despite the value of desmopressin testing during IPSS as a diagnostic tool to differentiate CD and EAS (31), this procedure in no way allows the determination of the side of the adenoma. We found low sensitivity, equal to 50% of cases, in keeping with previously published series (10, 25, 26). This result can probably be explained by a pre-existing communication between the cavernous sinuses or by a contralateral drainage dominance of one side (32). Prediction of the lateralization of the adenoma with petrosal sinus sampling can be biased by the catheter position or abnormal venous drainage, and this point cannot be modified by the type of secretagog used, desmopressin or CRH.

As very few data are published for the use of desmopressin during petrosal sinus sampling, our study confirms the role of this procedure in the differential diagnosis of ACTH-dependent Cushing's syndrome. Indeed, few patients presenting EAS had previously been evaluated with this procedure (Table 3). Adding the seven patients reported in this series, desmopressin stimulation during petrosal sinus sampling currently presents with a specificity of 100%, and a sensitivity exceeding 90%, comparing well with the results obtained with CRH stimulation. Comparison with recently described combined CRH and desmopressin stimulation petrosal sinus sampling is difficult as only few studies are published on these procedures (33). However, as shown in Table 3, combining both secretagogues may improve the sensitivity of the procedure. Other studies will be necessary to better evaluate the accuracy of each procedure, particularly concerning ectopic ACTH secretion, as only few cases have been evaluated since then.

The wide availability of desmopressin compared with CRH and the high sensitivity and specificity of desmopressin-stimulated petrosal sinus sampling make it a valuable alternative method in the differential diagnosis of ACTH-dependent Cushing's syndrome.

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