SIMPOSIO 1

UN ASPETTO PECULIARE DELLA DIAGNOSI: LA DIAGNOSI DIFFERENZIALE TRA CUSHING IPOFISARIO E CUSHING ECTOPICO

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Approach to the Patient with Possible Cushing's Syndrome

Marco Boscaro and Giorgio Arnaldi

J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

The differential diagnosis of ACTH-dependent CS remains one of the more challenging issues in clinical endocrinology

TABLE 1. Causes of Cushing's syndrome (data based on the authors' patient population; n = 423)

Diagnosis	Patient (%)
ACTH-dependent	
Pituitary-dependent Cushing's syndrome (Cushing disease)	65
Ectopic ACTH syndrome (*i.e.* bronchial, thymic, pancreatic carcinoids, medullary thyroid carcinoma, *etc.*)	7
Ectopic CRH syndrome	<1
ACTH-independent	
Adrenal adenoma	18
Adrenal carcinoma	6
PPNAD (including the Carney complex)	1
AIMAH (aberrant expression of ectopic and eutopic membrane receptors: gastric inhibitory polypeptide, catecholamines, or LH/human chorionic gonadotropin, vasopressin, and serotonin)	3

Diagnosis and Management of Cushing's Syndrome: Results of an Italian Multicentre Study*

CECILIA INVITTI, FRANCESCA PECORI GIRALDI, MARTINA DE MARTIN, FRANCESCO CAVAGNINI, AND THE STUDY GROUP OF THE ITALIAN SOCIETY OF ENDOCRINOLOGY ON THE PATHOPHYSIOLOGY OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS†

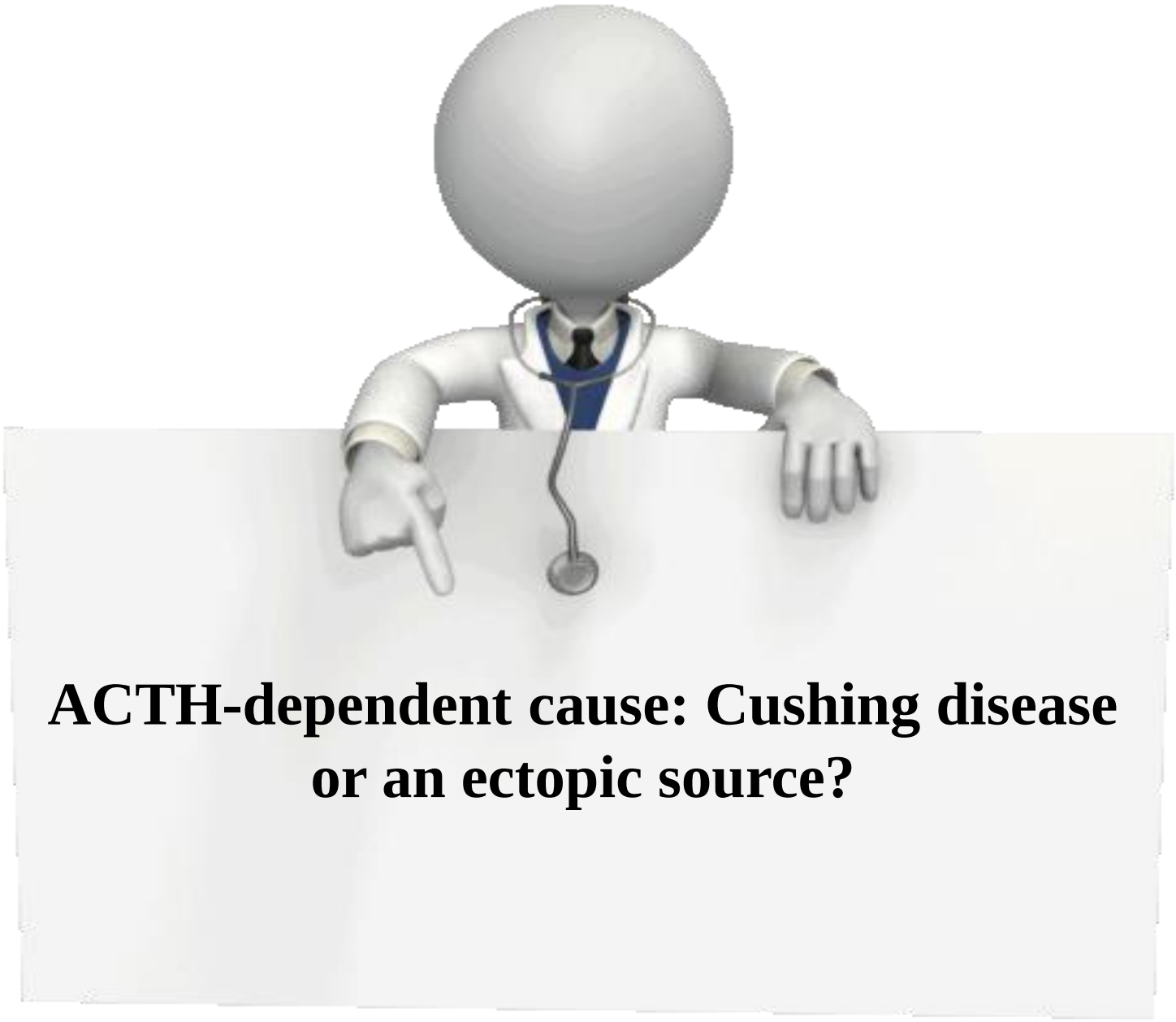
(*J Clin Endocrinol Metab* **84:** 440–448, 1999)

TABLE 1. Patient distribution and demographic data

	Cushing's disease	Adrenal adenoma	Adrenal carcinoma	Ectopic ACTH/CRH secretion	Nodular adrenal hyperplasia
Number of patients	288	80	24	25	9
Mean age at diagnosis (yr)	36 ± 0.8	37 ± 1.3	41 ± 3.1	44 ± 3.6	35 ± 6.1
Range	11–72	15–67	1.2–65	14–71	0.5–62
Sex (F/M)	239/49	75/5	14/10	10/15	7/2
Time between first symptoms and diagnosis (months)	29 ± 1.7	27 ± 2.8	13 ± 4.8	18 ± 4.7	22 ± 4.8

In women with ACTH dependent Cushing's syndrome, CD is 20-fold more prevalent than ectopic CS, while in men the ratio is 3:1.

In women with ACTH-dependent Cushing's syndrome, the *pretest probability* of Cushing's disease is about 90%, thus any test should improve on these probabilities to have added value.



ACTH-dependent cause: Cushing disease or an ectopic source?

Cushing's syndrome: from physiological principles to diagnosis and clinical care

J Physiol 593.3 (2015) pp 493–506

Hershel Raff[1,2] and Ty Carroll[3]

ACTH

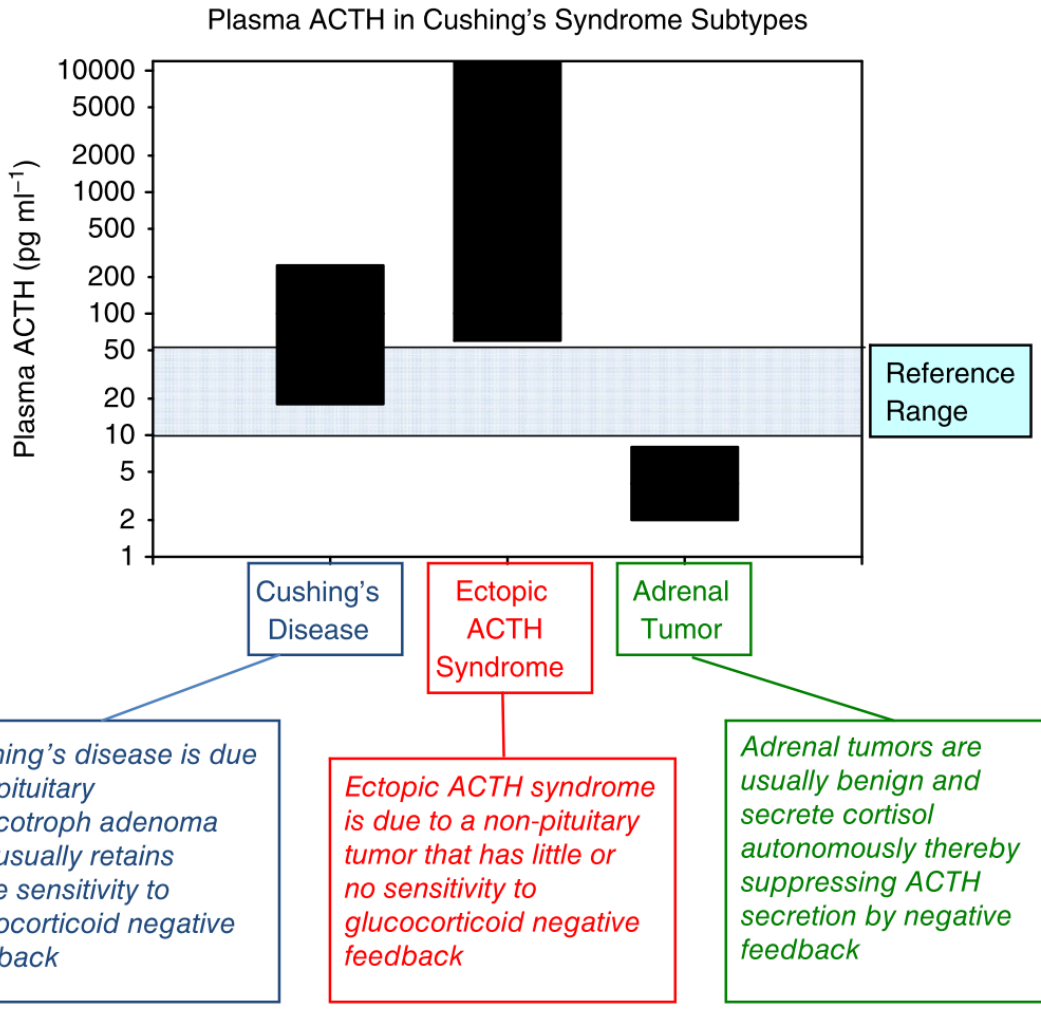


Figure 5. Plasma ACTH in Cushing's syndrome subtypes
Plasma ACTH concentrations (pg ml^{-1}) in patients with ACTH-dependent Cushing's syndrome (Cushing's disease (pituitary corticotroph adenomas) and ectopic ACTH) and ACTH-independent Cushing's syndrome (adrenal tumour). Note that plasma ACTH is within the reference range (blue shading) in many patients with Cushing's disease and that, on average, patients with ectopic ACTH have very high plasma ACTH. Furthermore, patients with adrenal autonomy usually have suppressed plasma ACTH due to increased cortisol negative feedback suppression of the hypothalamus and pituitary. To convert to pmol l^{-1}, multiply pg ml^{-1} by 0.2202. From Raff *et al.* (2014) with permission.

Cushing's Syndrome Due to Ectopic Corticotropin Secretion: Twenty Years' Experience at the National Institutes of Health

The Journal of Clinical Endocrinology & Metabolism 90(8):4955–4962

doi: 10.1210/jc.2004-2527

Ioannis Ilias, David J. Torpy, Karel Pacak, Nancy Mullen, Robert A. Wesley, and Lynnette K. Nieman

90 patients with EAS

TABLE 2. Baseline laboratory results from the initial visit of patients with CS caused by known or presumed ectopic ACTH secretion (unknown/occult)

	Units	Normal range	Patients with known source of ectopic ACTH secretion (69 of 73 patients)				Patients with unknown/occult source of ectopic ACTH secretion (16 of 17 patients)	
			Diagnosed within 6 months (n = 46)		Diagnosed after 6 months (n = 23)			
			Mean	Range	Mean	Range	Mean	Range
Serum K^+	mEq/liter (mmol/liter)	3.3–5.1 (3.3–5.1)	3.8 (3.8)	2.0–5.2 (2.0–5.2)	3.7 (3.7)	2.5–4.8 (2.5–4.8)	4.0 (4.0)	2.9–5.4 (2.9–5.4)
Urine cortisol	μg/24 h (nmol/d)	24–108 (70–300)	3,189 (8,810)	59–20,952 (160–57,620)	4,426 (12,170)	168–35,000 (460–96,250)	2,425 (6,670)	207–11,500 (570–31,770)
Urine 17OH corticosteroids	mg/24 h (mol/24 h)	2.0–10.0 (6–28)	53.3 (147)	1.8–193 (5–532)	55.1 (152)	12.4–113.5 (34–313)	40.3 (111)	5.4–161 (15–444)
Plasma ACTH	pg/ml (pmol/liter)	9–52 (2–11)	205.5 (45)	12.7–3,300 (3–724)	108.8 (24)	12.1–444 (3–97)	116.3 (26)	13.1–723 (3–159)

Patients who had undergone bilateral adrenalectomy are excluded. Values are in conventional units; values in SI units are in *parentheses*.

An extraordinarily high serum ACTH levels (>110 pmol/L, >500 pg/ml) would usually indicate an ectopic ACTH production as the causative pathology.

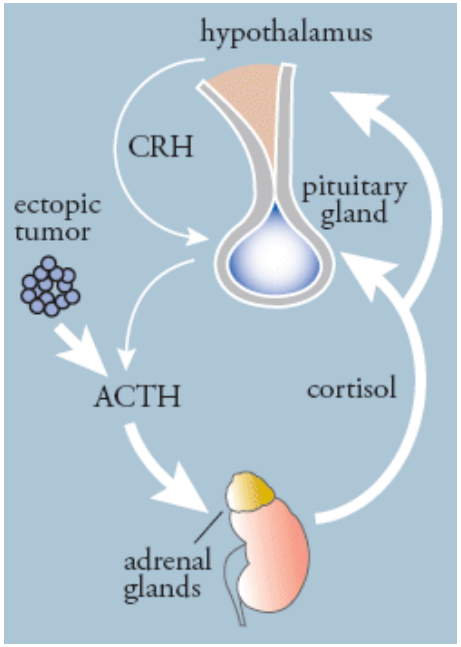
Although ACTH and serum cortisol levels tend to be higher in EAS than in CD, there is a considerable overlap between the two conditions.

In EAS basal plasma ACTH levels may be normal in around 32% of patients

Ectopic ACTH Syndrome

ANDREA M. ISIDORI
ANDREA LENZI

Arq Bras Endocrinol Metab 2007;51/8



Tumours causing **EAS** are usually characterized by their ***unresponsiveness*** **to glucocorticoid feedback, CRH or desmopressin responsiveness**.

Cushing's Syndrome

ENDOCRINOLOGY AND METABOLISM CLINICS OF NORTH AMERICA

Endocrinol Metab Clin N Am
37 (2008) 135–149

Rosario Pivonello, MD, PhD*,
Maria Cristina De Martino, MD, Monica De Leo,
Gaetano Lombardi, MD, Annamaria Colao, MD,

High dose DST (HDDST)

High doses of glucocorticoids partially suppress ACTH secretion from most corticotroph pituitary tumors, whereas ectopic tumors are generally resistant to feedback inhibition. There are several versions of the HDDST, including the **standard 2 days' oral high dose** (2 mg every 6 h for eight doses), the **8-mg overnight oral**, and the **intravenous (IV) 4- to 7-mg tests**. Plasma and/or urinary cortisol levels are evaluated before, during, and/or after dexamethasone administration.

Effectiveness *Versus* Efficacy: The Limited Value in Clinical Practice of High Dose Dexamethasone Suppression Testing in the Differential Diagnosis of Adrenocorticotropin-Dependent Cushing's Syndrome

J Clin Endocrinol Metab **82:** 1780–1785, 1997

DAVID C. ARON, HERSHEL RAFF, AND JAMES W. FINDLING

112 consecutive patients with ACTH-dependent Cushing's syndrome (95 CD, 17 ECS)

TABLE 2. Characteristics of patients stratified by whether high dose dexamethasone suppression (HDD) testing was performed

	Patients who underwent HDD	Patients who did not undergo HDD	*P*
n	73	39	0.195[a]
Age	43.2 ± 15.7	39.7 ± 13.8	
Sex (% female)	63.0	76.9	0.133[b]
Duration (months)	33.4 ± 27.3	39.5 ± 37.3	0.645[a]
% with hypokalemia	15.3	13.5	0.805[b]
24-h urinary free cortisol (nmol/day)	2615 ± 6215	1241 ± 2127	0.002[a]
Plasma ACTH (pmol/L)	21 ± 22	22 ± 24	0.651[a]
% with ectopic ACTH syndrome	20.5	5.1	0.030[b]

Conversion factors: urinary free cortisol: μg/24 h = 0.3625 × nmol/day; Plasma ACTH: pg/mL = 4.5 × pmol/L.
[a] By Mann-Whitney U test.
[b] By Pearson χ^2 test.

Based upon the standard criterion (i.e. serum cortisol suppression by 50% or more of the baseline):

- **Sensitivity: 81%**
- **Specificity: 66.7%**

Indeed **22–40%** of **EAS** patients demonstrate either serum or urinary 17-OHCS **suppression** on **HDDST**. Patients with ***bronchial carcinoids*** seem to show a significant degree of cortisol suppression (approximately 60%) following the HDDST.

Approach to the Patient with Possible Cushing's Syndrome

Marco Boscaro and Giorgio Arnaldi

J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

Although the HDDST showed a relatively high sensitivity in identifying patients with Cushing's disease, its specificity is low and in clinical practice has little diagnostic utility whatever the protocol and the cutoff of cortisol suppression used. In accord with other authors, we do not recommend the routine use of HDDST alone in the differential diagnosis of Cushing's syndrome (42, 44, 45).

J Clin Endocrinol Metab **84:** 440–448, 1999

Diagnosis and Management of Cushing's Syndrome: Results of an Italian Multicentre Study*

CECILIA INVITTI, FRANCESCA PECORI GIRALDI, MARTINA DE MARTIN, FRANCESCO CAVAGNINI, AND THE STUDY GROUP OF THE ITALIAN SOCIETY OF ENDOCRINOLOGY ON THE PATHOPHYSIOLOGY OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS†

TABLE 2. Performance characteristics of tests used for the differential diagnosis of ACTH-dependent Cushing's syndrome

Criteria adopted	Sensitivity	Specificity	Diagnostic accuracy	Predictive values	
				Positive	Negative
CRH					
ACTH increase by 50%	85%	100%	86%	100%	36%
Cortisol increase by 50%	59%	92%	61%	99%	15%
Dexamethasone, 8 mg					
Cortisol suppression by 80%	56%	100%	63%	100%	31%
UFC suppression by 80%	47%	100%	50%	100%	10%
IPSS C:P gradient					
Basal ≥2	81%	90%	82%	96%	36%
After CRH ≥3	85%	100%	87%	100%	45%

IPSS, Inferior petrosal sinus sampling.

An 80% decrease in UFC or plasma cortisol can be observed only in patients with CD; however, this criterion is burdened by a low sensitivity.

Discriminatory Value of the Low-Dose Dexamethasone Suppression Test in Establishing the Diagnosis and Differential Diagnosis of Cushing's Syndrome

J Clin Endocrinol Metab, November 2003, 88(11):5299–5306

ANDREA M. ISIDORI, GREGORY A. KALTSAS, SHAHID MOHAMMED, DAMIAN G. MORRIS, PAUL JENKINS, SHERN L. CHEW, JOHN P. MONSON, G. MICHAEL BESSER, AND ASHLEY B. GROSSMAN

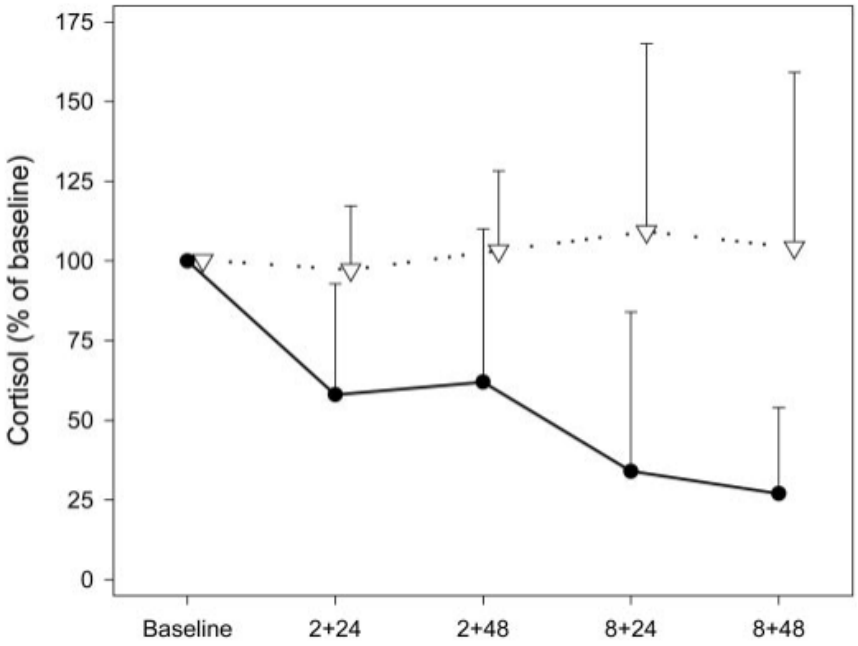


FIG. 2. Percentage change of serum cortisol levels during the consecutive LDDST+HDDST in 135 patients with CD (●) and 29 patients with ectopic ACTH-syndrome (△). The time of blood sample collection is shown as 2 + 24: at 0900 h after 24 h of 2 mg/d; 2 + 48: at 0900 h after 48 h of 2 mg/d; 8 + 24: at 0900 h after 24 h of 8 mg/d; 8 + 48: at 0900 h after 48 h of 8 mg/d.

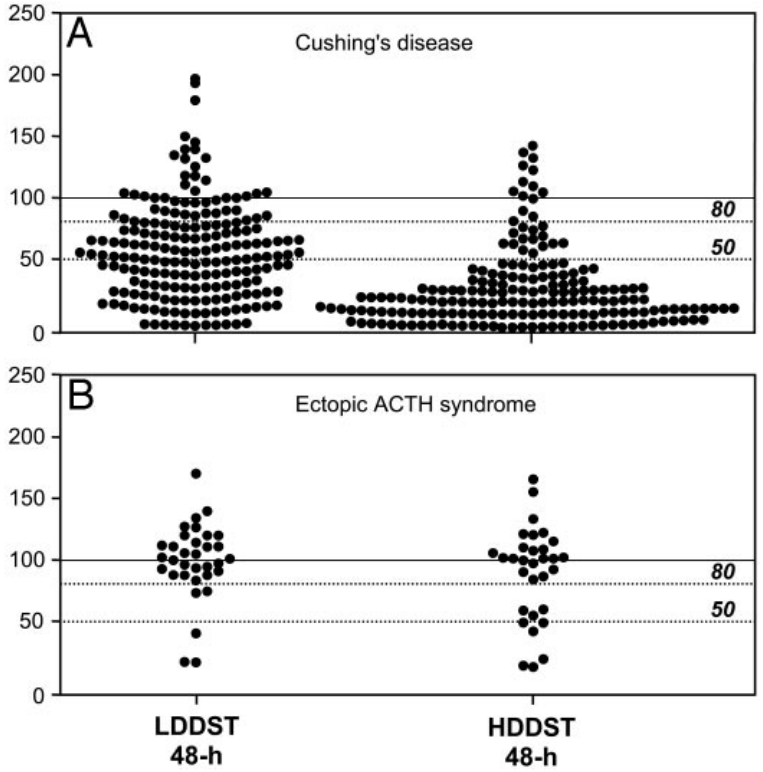


FIG. 1. Percentage of baseline of serum cortisol levels 48 h after 2 mg/d dexamethasone (LDDST 48 h) or 8 mg/d dexamethasone (HDDST 48 h) according to the etiology of CS.

In the LDDST, serum cortisol levels do not change significantly in ectopic CS but suppress by 30% in patients with CD, predicting CS secondary to ACTH secreting pituitary adenoma with a sensitivity of 82% and specificity of 79%.

There was no further significant suppression of cortisol from the 24 hour to 48 hour value on both LDDST and HDDST

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Marco Boscaro and Giorgio Arnaldi

J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

Although the CRH test is considered the most reliable dynamic noninvasive test for the differential diagnosis of ACTH-dependent Cushing's syndrome, this test cannot make a 100% differentiation between pituitary and ectopic causes. From literature data, the sensitivity and specificity using ACTH criteria is approximately 90% (9, 11, 42). Unfortunately, there is yet no consensus on the criteria for interpreting the test as positive. Variability in interpretation depends on the type of CRH used (usually ovine in the United States and human in Europe), the weight-based (1 μg/kg) or the 100-μg fixed dose, and the wide range of response parameters (increase above baseline in peak ACTH, 30–50%, *vs.* peak cortisol, 14–20%) (9, 11, 42).

A Simplified Morning Ovine Corticotropin-Releasing Hormone Stimulation Test for the Differential Diagnosis of Adrenocorticotropin-Dependent Cushing's Syndrome

J Clin Endocrinol Metab 77: 1308-1312, 1993

LYNNETTE K. NIEMAN, EDWARD H. OLDFIELD*, ROBERT WESLEY†, GEORGE P. CHROUSOS‡, D. LYNN LORIAUX§, AND GORDON B. CUTLER, JR.‡

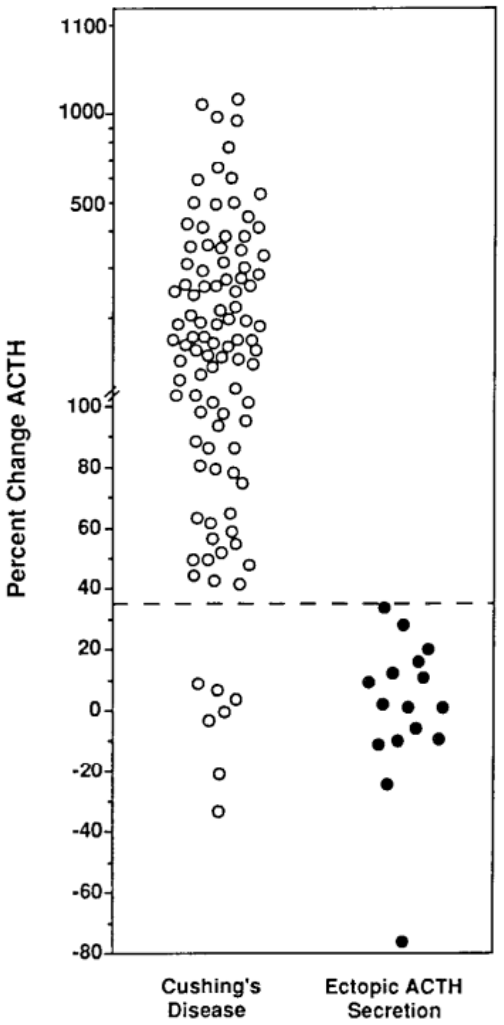


FIG. 2. Responses of plasma ACTH to CRH in 100 patients with Cushing's disease and 16 patients with ectopic ACTH secretion. Responses are expressed as the percent change in mean ACTH concentration 15 and 30 min after ovine CRH administration from the mean basal value 1 and 5 min before the injection. The *dashed line* indicates a response of 35%.

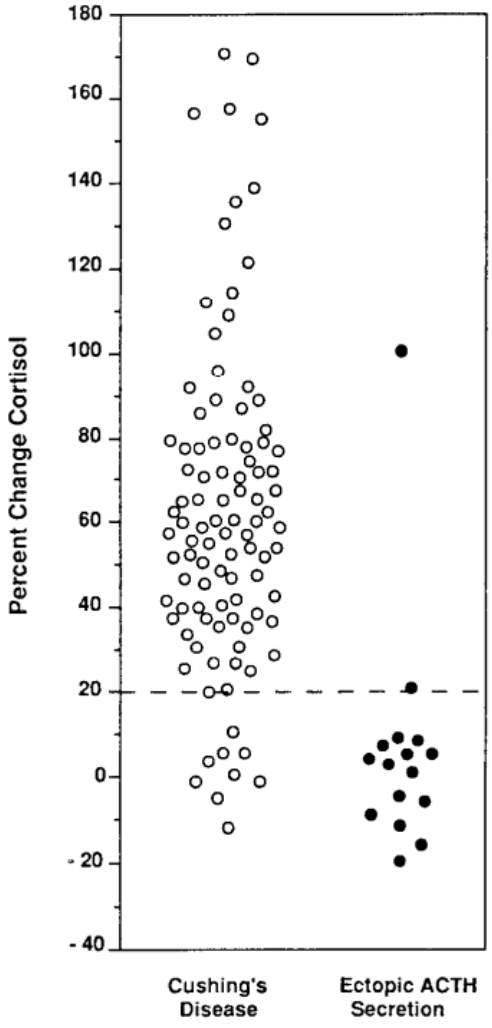


FIG. 3. Responses of plasma cortisol to CRH in 98 patients with Cushing's disease and 16 patients with ectopic ACTH secretion. Responses are expressed as the percent change in the mean cortisol concentration 30 and 45 min after ovine CRH treatment from the mean basal value 1 and 5 min before the injection. The *dashed line* indicates a response of 20%.

With the classic ovine CRH stimulation test:

- **An increase in *ACTH* >35% and in *cortisol* >20% above baseline levels is considered to be a specific response for CD**
- **ACTH: sensitivity (93%), specificity (100%).**
- **Cortisol: sensitivity (91%), specificity (88%).**

Optimal Response Criteria for the Human CRH Test in the Differential Diagnosis of ACTH-Dependent Cushing's Syndrome

J Clin Endocrinol Metab, April 2002, 87(4):1640–1645

J. NEWELL-PRICE, D. G. MORRIS, W. M. DRAKE, M. KORBONITS, J. P. MONSON, G. M. BESSER, AND A. B. GROSSMAN

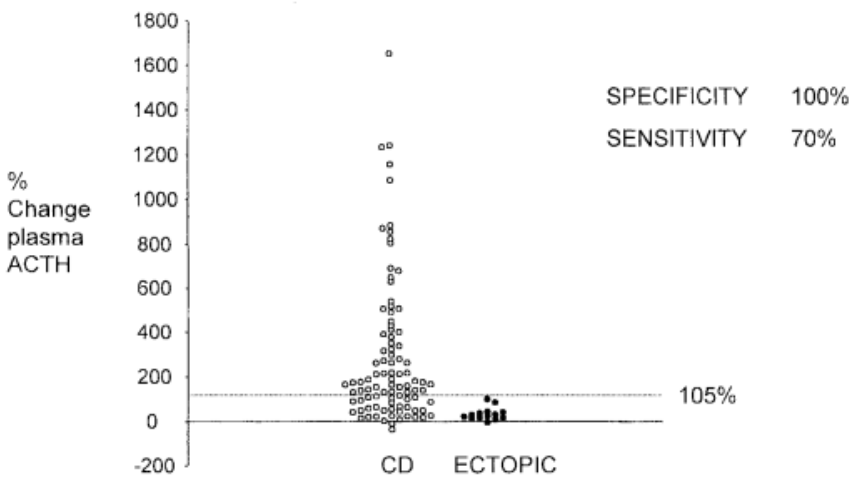


FIG. 5. Percentage change in plasma ACTH from a mean basal at −15 and 0 min to the maximum value after the administration of hCRH (100 μg iv) in 94 patients with CD and 14 patients with the EC.

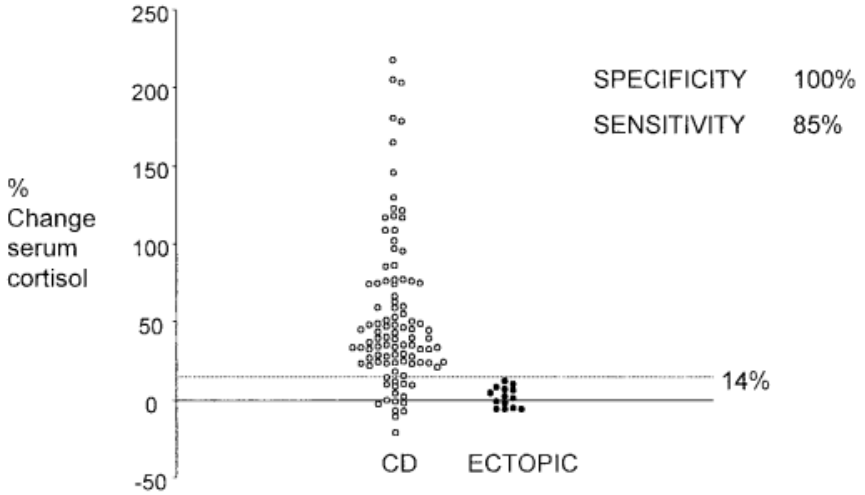


FIG. 3. Percentage change in serum cortisol from a mean basal at −15 and 0 min to a mean value calculated from the levels at 15 and 30 min after the administration of hCRH (100 μg iv) in 100 patients with CD and 14 patients with the EC.

With the classic human CRH stimulation test, an increase in ACTH >105% and cortisol >14% is considered to be a specific response for CD.

Cushing's Syndrome Due to Ectopic Corticotropin Secretion: Twenty Years' Experience at the National Institutes of Health

The Journal of Clinical Endocrinology & Metabolism 90(8):4955–4962

doi: 10.1210/jc.2004-2527

Ioannis Ilias, David J. Torpy, Karel Pacak, Nancy Mullen, Robert A. Wesley, and Lynnette K. Nieman

The Ectopic Adrenocorticotropin Syndrome: Clinical Features, Diagnosis, Management, and Long-Term Follow-Up

The Journal of Clinical Endocrinology & Metabolism 91(2):371–377

doi: 10.1210/jc.2005-1542

Andrea M. Isidori, Gregory A. Kaltsas, Carlotta Pozza, Vanni Frajese, John Newell-Price, Rodney H. Reznek, Paul J. Jenkins, John P. Monson, Ashley B. Grossman, and G. Michael Besser

However, **approximately 5–15% of patients with EAS have been shown to respond to CRH administration.**

Clinical and Biochemical Characteristics of Adrenocorticotropin-Secreting Macroadenomas

Y. Sammy Woo, Andrea M. Isidori, Winnie Z. Wat, Gregory A. Kaltsas, Fari Afshar, Ian Sabin, Paul J. Jenkins, John P. Monson, G. Michael Besser, and Ashley B. Grossman

J Clin Endocrinol Metab, August 2005, 90(8):4963–4969

TABLE 3. Responsivity to HDDST

	Macroadenomas	Microadenomas	*P* value
No. of patients with HDDST performed	17	174	
% suppression	57.6 ± 8.7 (95% CI, 39.2–76.0)	74.4 ± 2.1 (95% CI, 70.3–78.5)	0.02
% of patients having >50% suppression	64.7% (11/17)	87.4% (152/174)	0.023

CI, Confidence interval.

The presence of an *ACTH-secreting pituitary macroadenoma* could lead to a paradoxical diagnostic gap.

In these patients, responses to both CRH stimulus and HDSST test are more frequently negative.

TABLE 4. Cortisol responsivity to CRH stimulation test

	Macroadenomas	Microadenomas	*P* value
No. of patients	17	73	
% of cortisol rise from baseline	30.6 ± 9.7% (95% CI, 10.2–51.1%)	54.9 ± 6.0% (95% CI, 43.0–66.8%)	0.071
Positive CRH test response	64.7% (11/17)	83.6% (61/73)	0.097

CI, Confidence interval.

ACTH after 15 min distinguishes between Cushing's disease and ectopic Cushing's syndrome: a proposal for a short and simple CRH test

European Journal of Endocrinology
(2015) **173**, 197–204

Katrin Ritzel, Felix Beuschlein, Christina Berr, Andrea Osswald, Nicole Reisch, Martin Bidlingmaier, Harald Schneider, Jürgen Honegger[1], Lucas L. Geyer[2], Jochen Schopohl and **Martin Reincke**

Table 2 ROC curve characteristics of different test variables.

Test variable	Cutoff value (%)	ROC AUC (S.E.M.)	Positive LR	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Post-test probability (%)
ACTH (15 min)	**≥43**	**0.89 (0.03)**	**14.9**	**83**	**94**	**98**	**58**	**98**
ACTH (30 min)	**≥62**	0.91 (0.03)	13.9	77	94	98	50	98
ACTH (45 min)	**≥51**	0.89 (0.04)	12.5	69	94	98	40	98
ACTH (60 min)	**≥69**	0.85 (0.05)	8.0	42	94	97	30	97
Cortisol (15 min)	**≥41**	0.75 (0.06)	4.9	28	94	95	24	95
Cortisol (30 min)	**≥32**	0.87 (0.04)	10.9	59	94	98	37	98
Cortisol (45 min)	**≥50**	0.85 (0.05)	8.4	46	94	97	31	97
ACTH (15 min)+Cortisol (30 min)	**≥110**	0.90 (0.03)	13.4	74	94	98	48	98
ACTH (30 min)+Cortisol (30 min)	≥108	0.90 (0.03)	*12.8*	71	94	98	45	*98*
Δ_{max} ACTH (120 min)	**≥95**	0.90 (0.04)	*12.9*	71	94	98	46	*98*
Δ_{max} Cortisol (120 min)	**≥49**	0.88 (0.04)	*10.5*	55	94	97	35	*97*
AUC ACTH ($\%_B$)	**≥7375**	0.89 (0.04)	9.0	52	94	97	33	97
AUC Cortisol ($\%_B$)	**≥3040**	0.86 (0.05)	10.4	67	94	98	38	98
HDDS+$ACTH_{CRH\ 15\ min}$	**≥119**	0.94 (0.03)	11.2	72	93	98	53	98

AUC, area under the curve; +LR, positive likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

An increase in ACTH of ≥43% at 15 min after human CRH was the strongest predictor of CD. All of the other criteria of stimulated ACTH and cortisol levels were not superior in predicting CD.

The limited value of the desmopressin test in the diagnostic approach to Cushing's syndrome

Clinical Endocrinology (2001) **54**, 609–616

Massimo Terzolo*, Giuseppe Reimondo*, Anna Alì*, Giorgio Borretta†, Flora Cesario†, Anna Pia†, Piero Paccotti* and Alberto Angeli*

Table 2 Operating characteristics of the CRH test *vs.* the DDAVP test in the differential diagnosis of ACTH-dependent Cushing's syndrome

	CRH	DDAVP
ACTH $\Delta\% > 35\%$		
Sensitivity	90%	89%
Specificity	78%	40%
ACTH $\Delta\% > 35\%$ and $\Delta > 4{\cdot}5$ pmol/l		
Sensitivity	60%	89%
Specificity	78%	60%
ACTH $\Delta\% > 50\%$		
Sensitivity	90%	84%
Specificity	89%	40%
ACTH $\Delta\% > 50\%$ and $\Delta > 4{\cdot}5$ pmol/l		
Sensitivity	90%	84%
Specificity	89%	60%

Pituitary Published online: 28 May 2016

Second-line tests in the differential diagnosis of ACTH-dependent Cushing's syndrome

Mattia Barbot[1] · Laura Trementino[2] · Marialuisa Zilio[1] · Filippo Ceccato[1] · Nora Albiger[1] · Andrea Daniele[1] · Anna Chiara Frigo[3] · Rodica Mardari[4] · Giuseppe Rolma[4] · Marco Boscaro[1] · Giorgio Arnaldi[2] · Carla Scaroni[1]

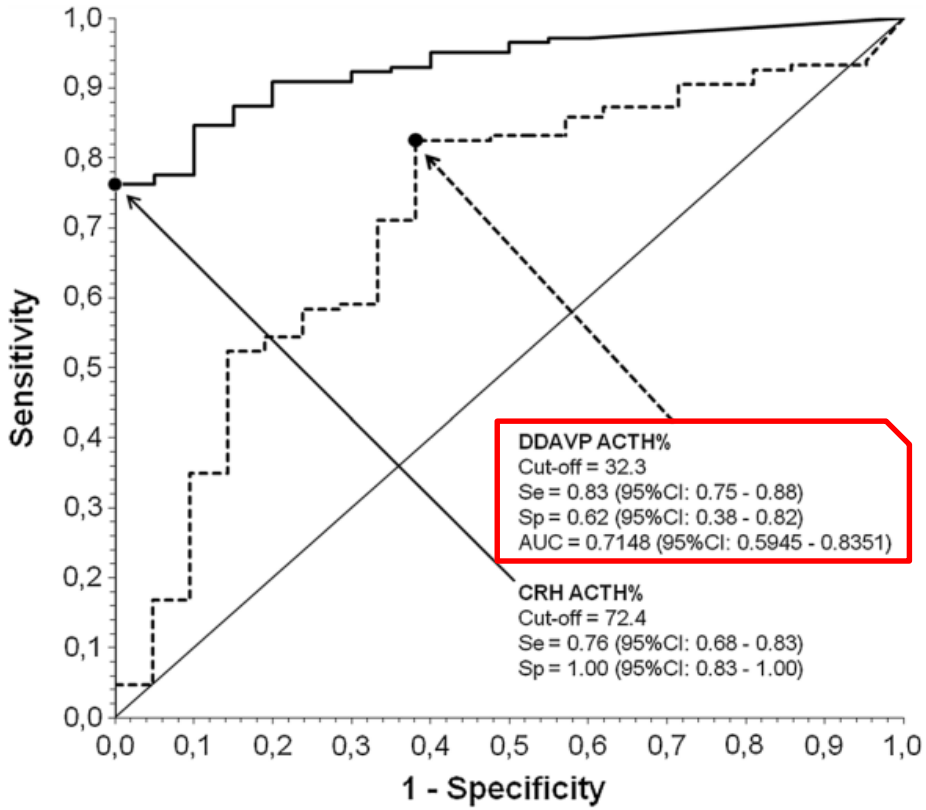


Fig. 2 ROC curves; optimal cut-off for the percentage increase in ACTH after the CRH test (*continuous line*) and after DDAVP test (*dotted line*) for the purpose of identifying patients with CD. The figure also shows the AUCs, SE and SP for the cut-off identified

The Desmopressin and Combined CRH-Desmopressin Tests in the Differential Diagnosis of ACTH-Dependent Cushing's Syndrome: Constraints Imposed by the Expression of V2 Vasopressin Receptors in Tumors with Ectopic ACTH Secretion

The Journal of Clinical Endocrinology & Metabolism 87(4):1646–1653

S. TSAGARAKIS, C. TSIGOS, V. VASILIOU, P. TSIOTRA, J. KASKARELIS, C. SOTIROPOULOU, S. A. RAPTIS, AND N. THALASSINOS

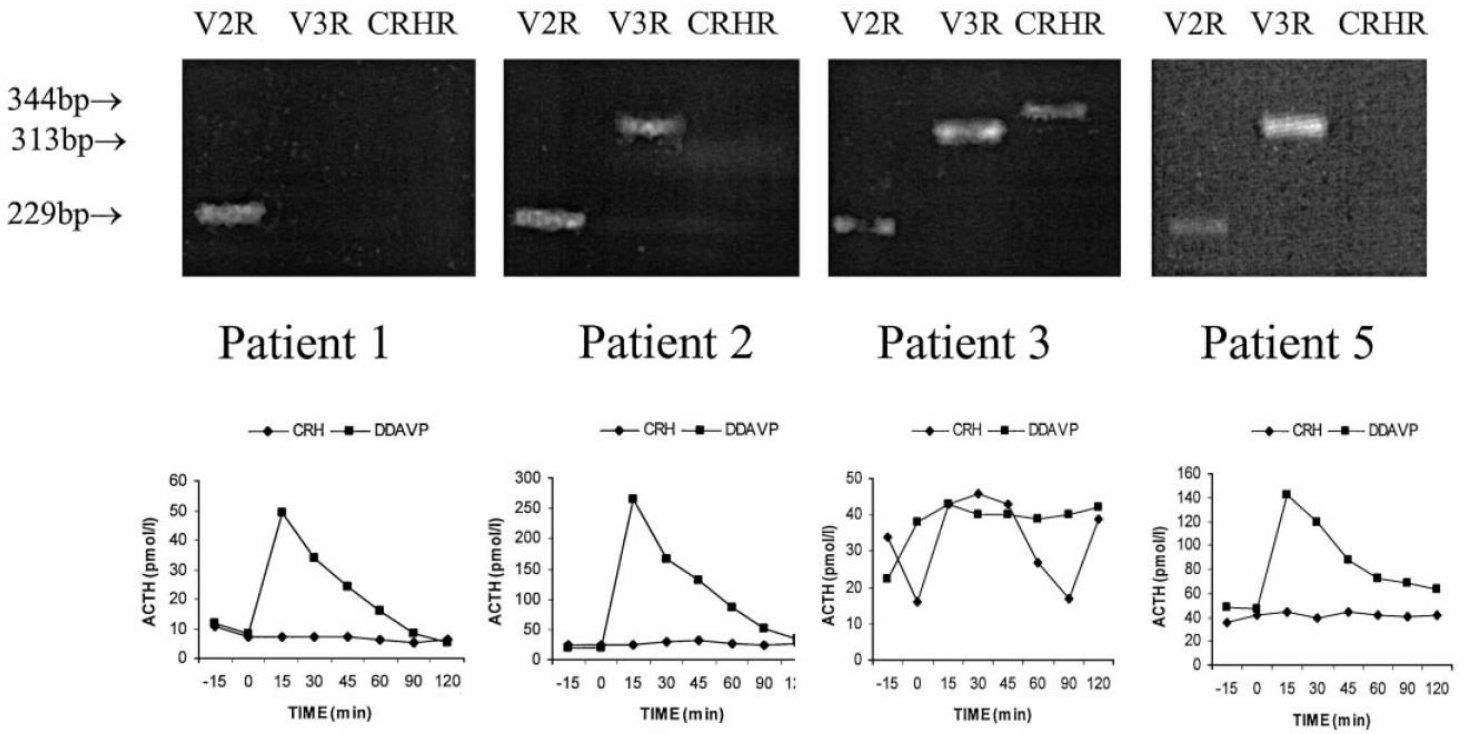


FIG. 6. *Top*, RT-PCR of V2R, V3R, and CRHR mRNA in the tumors from EAS patients 1, 2, 3, and 5. The expected size and position of the bands are indicated by the *arrows*. The specificity of the PCR signal for all three receptors was confirmed with enzyme restriction (data not shown). *Bottom*, Corresponding plasma ACTH responses to CRH and desmopressin (DDAVP) in the EAS patients. Note the erratic ACTH secretion in patient 3 that makes assessment of the responses to CRH and DDAVP rather perplexing.

Patients with EAS eventually also show a response, varying from 20-40%

The Desmopressin and Combined CRH-Desmopressin Tests in the Differential Diagnosis of ACTH-Dependent Cushing's Syndrome: Constraints Imposed by the Expression of V2 Vasopressin Receptors in Tumors with Ectopic ACTH Secretion

The Journal of Clinical Endocrinology & Metabolism 87(4):1646–1653

S. TSAGARAKIS, C. TSIGOS, V. VASILIOU, P. TSIOTRA, J. KASKARELIS, C. SOTIROPOULOU, S. A. RAPTIS, AND N. THALASSINOS

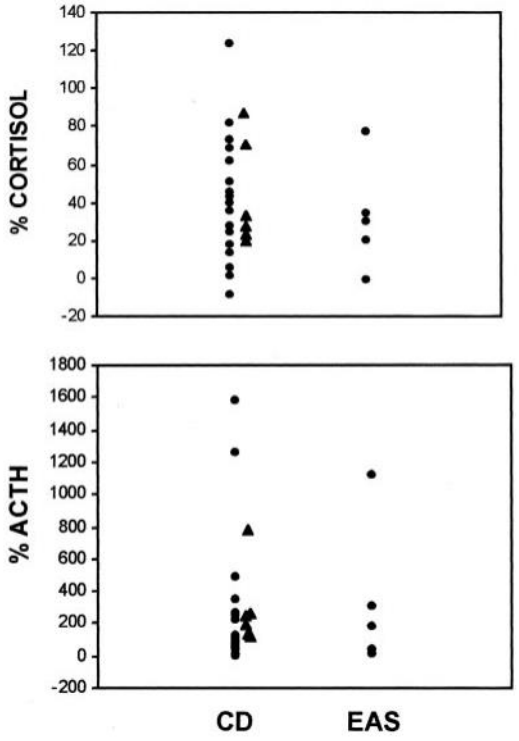


FIG. 1. Percent cortisol (*top*) and ACTH (*bottom*) responses after desmopressin administration in the patients with CD and histologically confirmed EAS. *Triangles* represent data from the six patients with CD, who were not operated (n = 2) or were not cured after transsphenoidal surgery (n = 4).

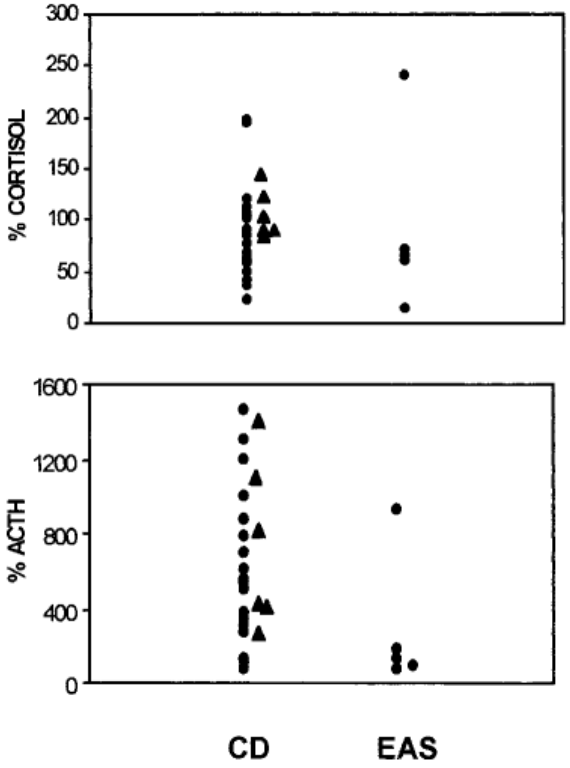
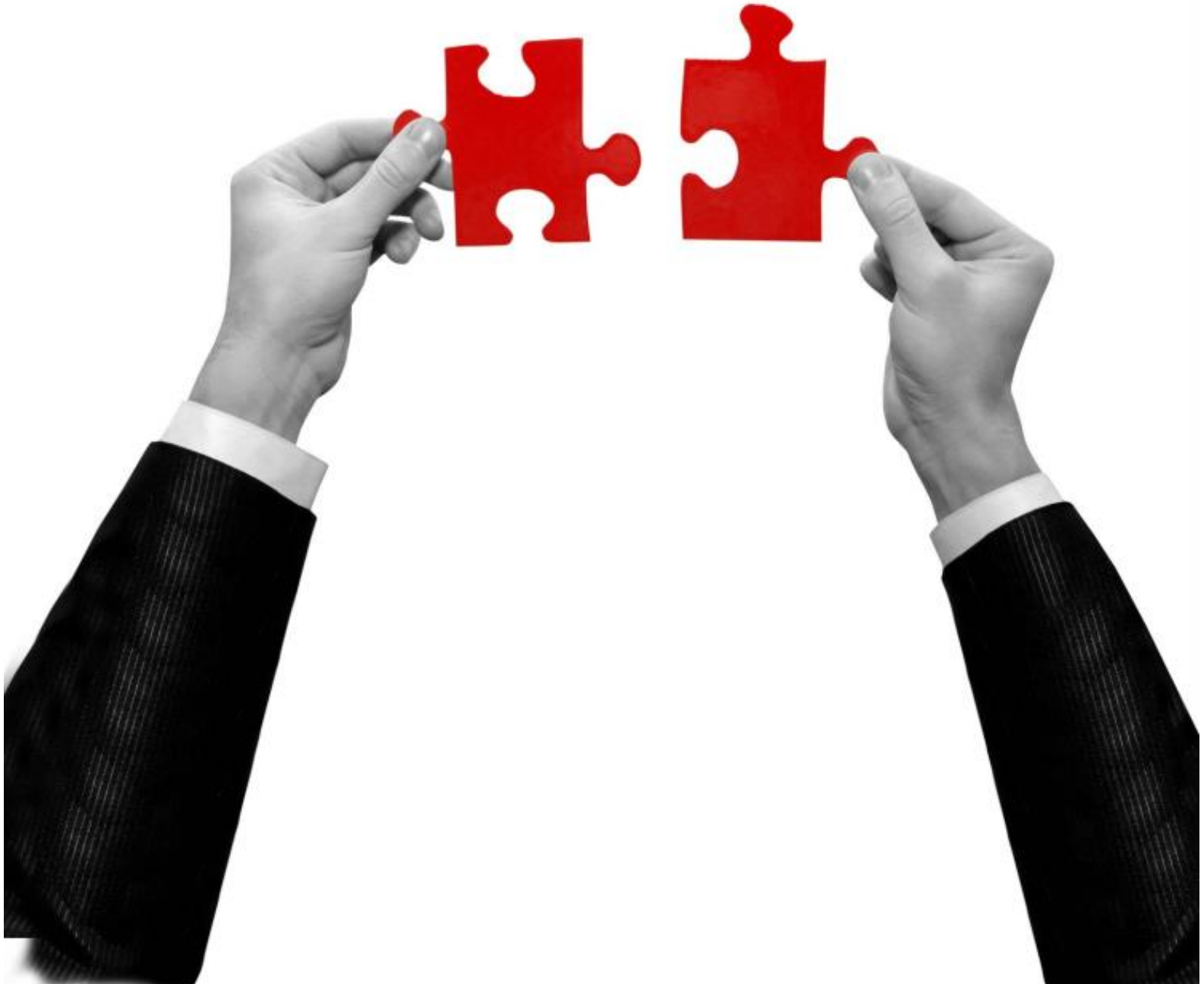


FIG. 4. Percent cortisol (*top*) and ACTH (*bottom*) responses after CRH plus desmopressin administration in the patients with CD and histologically confirmed EAS. *Triangles* represent data from the six patients with CD, who were not operated (n = 2) or were not cured after transsphenoidal surgery (n = 4).



Pituitary Published online: 28 May 2016

Second-line tests in the differential diagnosis of ACTH-dependent Cushing's syndrome

Mattia Barbot[1] · Laura Trementino[2] · Marialuisa Zilio[1] · Filippo Ceccato[1] · Nora Albiger[1] · Andrea Daniele[1] · Anna Chiara Frigo[3] · Rodica Mardari[4] · Giuseppe Rolma[4] · Marco Boscaro[1] · Giorgio Arnaldi[2] · Carla Scaroni[1]

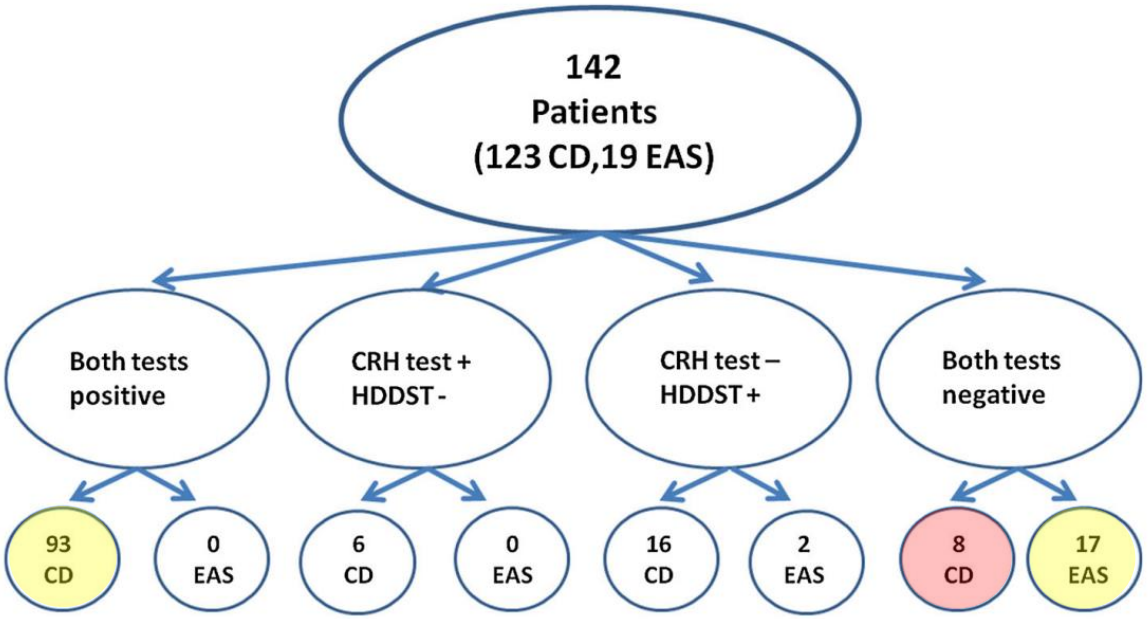


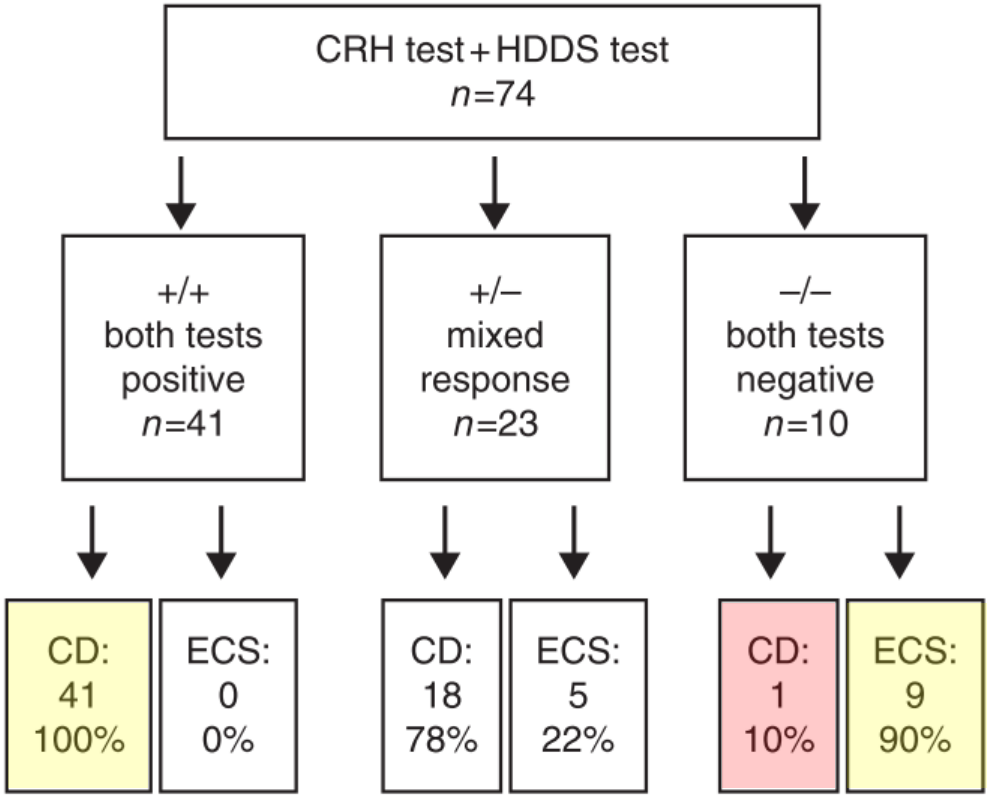
Fig. 3 Combined response to the CRH test (ACTH percentage increase >72.4 %) and the HDDST (cortisol suppression >52.7 %) in patients with CD and EAS

- **Patients with CD showed a stronger response to HDDST and CRH, and the adopted cut-offs showed a good SE and SP in discriminating them from patients with EAS. *Concordant tests indicated CD when positive*, whereas *no response to either test was highly suggestive of EAS*.**
- ***The DDAVP test* was of limited utility in the diagnostic phase. DDAVP test may play a support role only *in case of discordant results of the other two tests.* The DDAVP test was assessed in patients with a CRH test + and HDDST -: a positive response to both the CRH and the DDAVP tests correctly identified CD patients in 5/6 cases.**

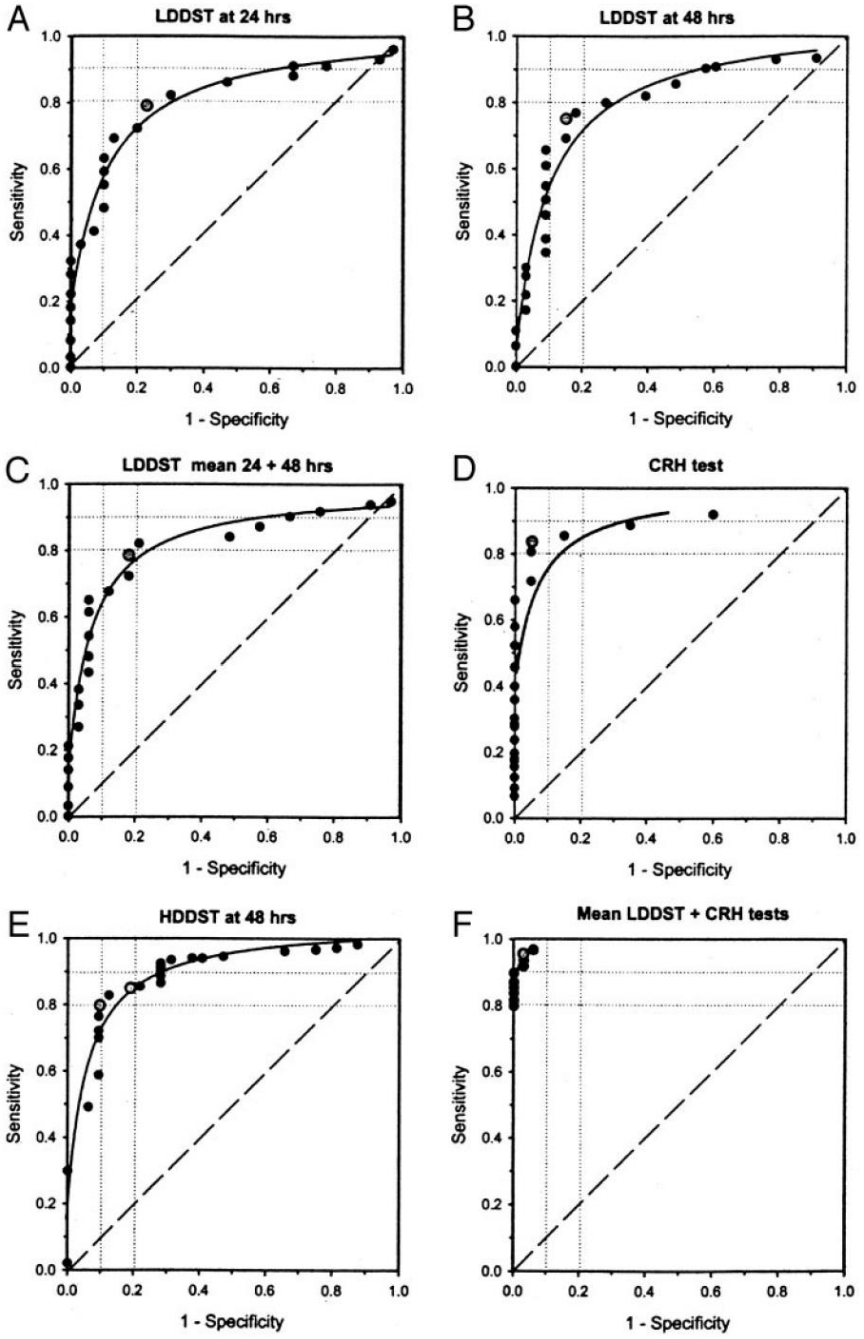
ACTH after 15 min distinguishes between Cushing's disease and ectopic Cushing's syndrome: a proposal for a short and simple CRH test

European Journal of Endocrinology
(2015) **173**, 197–204

Katrin Ritzel, Felix Beuschlein, Christina Berr, Andrea Osswald, Nicole Reisch, Martin Bidlingmaier, Harald Schneider, Jürgen Honegger[1], Lucas L. Geyer[2], Jochen Schopohl and **Martin Reincke**



The addition of cortisol suppression by dexamethasone did not increase the discriminatory power, but it is helpful for excluding ECS when both tests are positive.



Discriminatory Value of the Low-Dose Dexamethasone Suppression Test in Establishing the Diagnosis and Differential Diagnosis of Cushing's Syndrome

J Clin Endocrinol Metab, November 2003, 88(11):5299–5306

ANDREA M. ISIDORI, GREGORY A. KALTSAS, SHAHID MOHAMMED, DAMIAN G. MORRIS
PAUL JENKINS, SHERN L. CHEW, JOHN P. MONSON, G. MICHAEL BESSER, AND
ASHLEY B. GROSSMAN

LDDST
Sensitivity: 82%
Specificity: 79%.

HDDST
Sensitivity: 91%
Specificity: 80%

CRH
Sensitivity: 81%
Specificity: 95%

LDDST + CRH
Sensitivity: 97%
Specificity: 94%

FIG. 4. ROCs for the LDDST (A–C), the CRH (D), the 48 h of the HDDST (E), and the combined response of the LDDST and CRH (F) for all data.

Other tests

Other laboratory findings may be helpful in establishing a diagnosis of CD or EAS, although not conclusively: hypokalemia, present in 70% of EAS *vs.* 10% of CD patients due to cortisol mineralocorticoid activity in conditions of enzyme 11β-HSD2 saturation; extremely high plasma ACTH concentrations (> 400 to 500 pg/mL; > 88 to 110 pmol/L) in EAS; positive tumor markers in EAS (examples: calcitonin, gastrin, chromogranin, βhCG, alpha-fetoprotein, CEA, CA 19-9, CA 125) (1,167); and measurement of pro-opiomelanocortin (POMC) and/or ACTH precursors (168,169), which are commonly present in patients with EAS despite the poor availability of these measures.

Cushing's syndrome caused by an occult source: difficulties in diagnosis and management

Ashley B Grossman*, Philip Kelly, Andrea Rockall, Satya Bhattacharya, Ann McNicol and Tara Balwick

Table 3 Other biochemical parameters that are elevated in patients with ectopic ACTH syndrome.

Peptide, marker, or hormone (% of total cases in which it is present)	Notes
Calcitonin (<30)	Medullary thyroid carcinoma, pheochromocytoma, MEN2, carcinoid, SCC, NET, gastrinomas, occult disease
Gastrin (<30)	Islet-cell tumors
Glucagon (~8)	Islet-cell tumors
5-HIAA (<10)	Up to one quarter of bronchial carcinoids, midgut or hindgut carcinoids, NET
Somatostatin (0.5)	Islet-cell tumors
Pancreatic polypeptide, vasoactive intestinal peptide, β-hCG, α-fetoprotein, α-subunit, neuron-specific endolase, GHRH, CRH, and carcinoembryonic antigen	Sporadic cases

Abbreviations: 5-HIAA, 5-hydroxyl-indole-acetic acid; β-hCG, β human chorionic gonadotropin; ACTH, adrenocorticotropic hormone; CRH, corticotrophin-releasing hormone; GHRH, growth-hormone-releasing hormone; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumor; SCC, small-cell carcinoma of the lung.

Clinical Utility of Plasma POMC and AgRP Measurements in the Differential Diagnosis of ACTH-Dependent Cushing's Syndrome

J Clin Endocrinol Metab 99: E1838–E1845, 2014

Gabrielle Page-Wilson, Pamela U. Freda, Thomas P. Jacobs, Alexander G. Khandji, Jeffrey N. Bruce, Sandra T. Foo, Kana Meece, Anne White, and Sharon L. Wardlaw

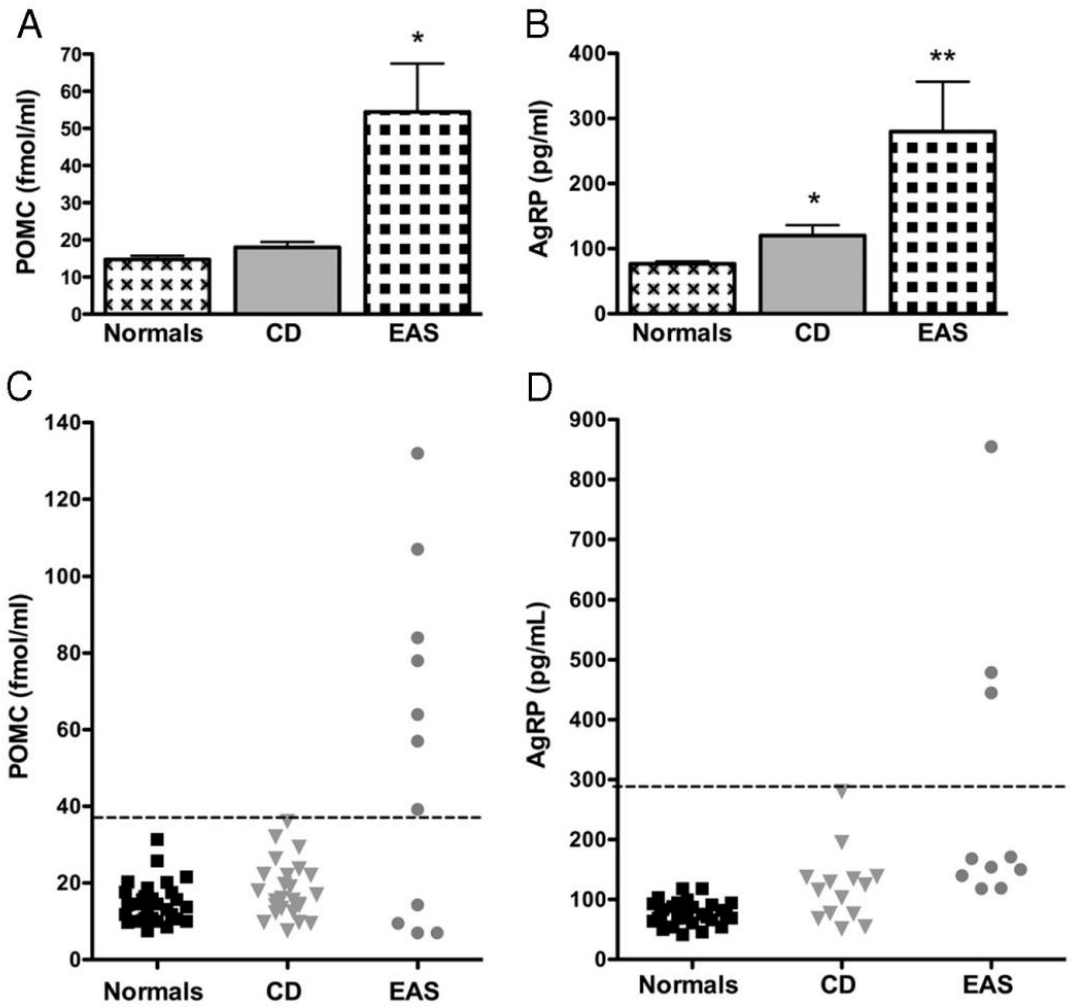


Figure 2. Mean POMC (A) and AgRP (B) levels in patients with CD, EAS, and normal controls (*, $P < .05$ and **, $P = .01$) and scatterplots of POMC (C) and AGRP (D) levels in patients with CD (▼), EAS (●), and normal controls (■). The dashed horizontal lines represent the diagnostic cutoff values, above which patients with EAS are identified.

The mean POMC and Agouti-related protein (AgRP) values were higher in EAS vs CD.

Although there was an overlap in POMC and AgRP levels between the groups, the POMC levels greater than 36 fmol/mL and AgRP levels greater than 280 pg/mL were specific for EAS.

When used together, they detected 9 of 11 cases of EAS, indicating that elevations in these peptides have a high positive predictive value for occult EAS.

CONCLUSIONS

- **Distinguishing between pituitary and ectopic ACTH secretion is still the most uncertain aspect of the diagnostic process.**
- **No single test is accurate enough to distinguish the ectopic from the pituitary sources of ACTH.**
- **The cutoff values identified for tests are often arbitrary and depend on the assay method used.**
- **It is crucial using multiple hormonal tests, imaging data and eventually bilateral inferior petrosal sinus sampling (BIPSS) for the differential diagnosis of a patient with Cushing's syndrome.**

Thank you for your attention

Approach to the Patient with Possible Cushing's Syndrome

Marco Boscaro and Giorgio Arnaldi

J Clin Endocrinol Metab, September 2009, 94(9):3121–3131

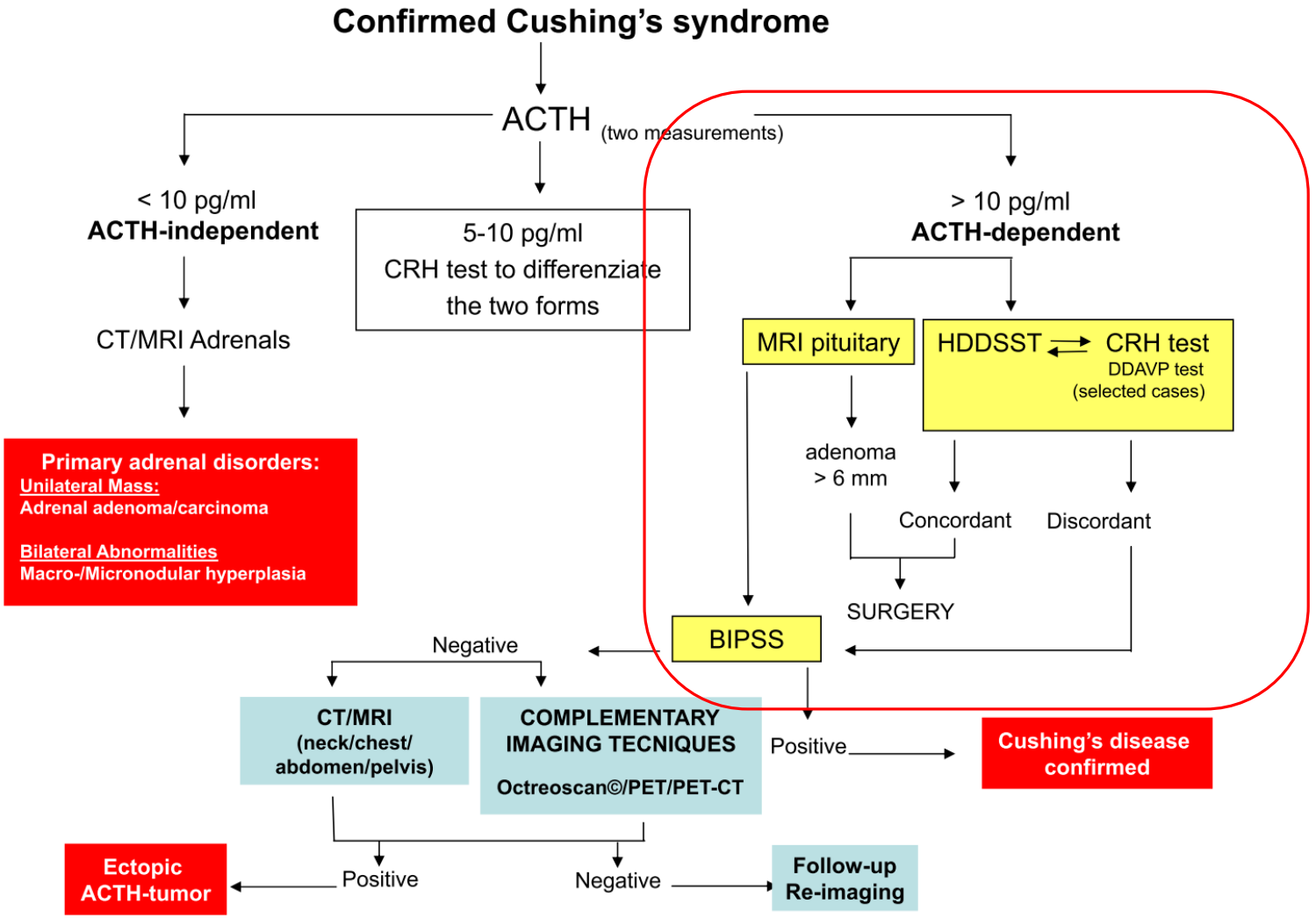


FIG. 1. Clinical decision-making flow chart.

Pituitary magnetic resonance imaging in Cushing's disease

Giovanni Vitale[1,2] · Fabio Tortora[3] · Roberto Baldelli[4] · Francesco Cocchiara[5] · Rosa Maria Paragliola[6] · Emilia Sbardella[7] · Chiara Simeoli[8] · Ferdinando Caranci[9] · Rosario Pivonello[8] · Annamaria Colao[8] on behalf of the A.B.C. Group

Endocrine (2017) 55:691–696
DOI 10.1007/s12020-016-1038-y

Clinical and biochemical findings suspicious for an ACTH-secreting pituitary adenoma

↓

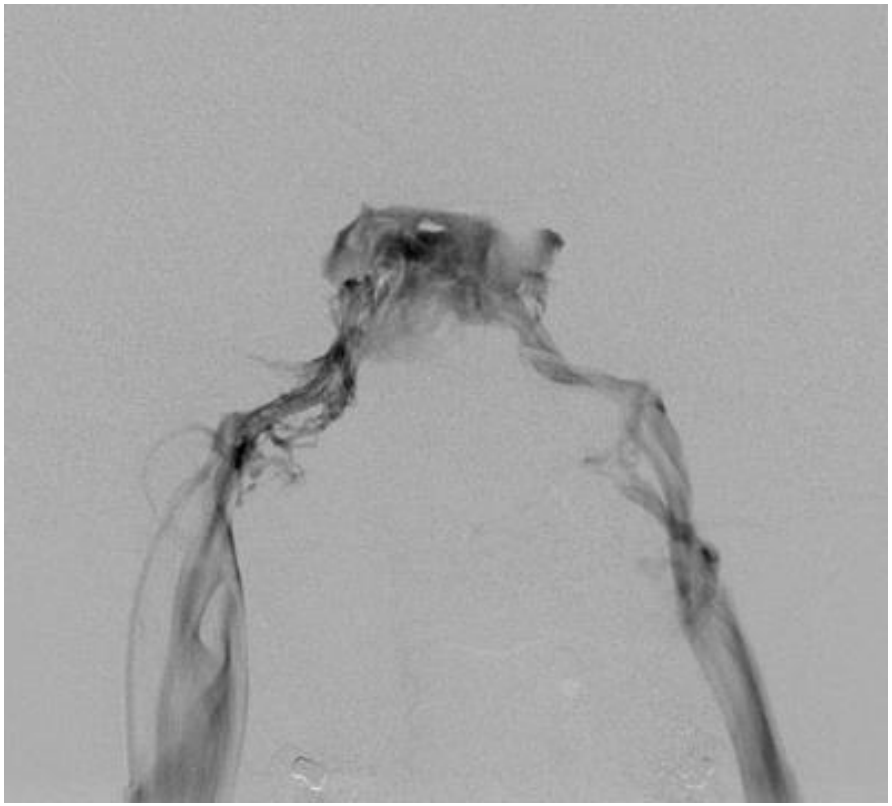
Pituitary MRI

	Coil Type	Plane	Mode	Pulse Sequence	TE	TR	FOV	Slice Thickness	Matrix Size
SAGITTAL T1	Head	SAG	2D	SE	10.3 ± 0.5 ms	400 ms	12-14 cm	1-1.5 mm	≥ 256x512
CORONAL T1	Head	COR	2D	SE	10.3 ± 0.5 ms	400 ms	12-14 cm	1-1.5 mm	≥ 256x512
CORONAL T2	Head	COR	2D	SE	100-120 ms	3000-4000 ms	14-18 cm	1-1.5 mm	≥ 256x512
CORONAL DINAMIC	Head	COR	2D	SE	17 ms	400 ms	12-14 cm	1-1.5 mm	256x192
SAGITTAL T1 POST FS	Head	SAG	2D	SE	10.3 ± 0.5 ms	400 ms	12-14 cm	1-1.5 mm	≥ 256x512
CORONAL T1 POST FS	Head	COR	2D	SE	10.3 ± 0.5 ms	400 ms	12-14 cm	1-1.5 mm	≥ 256x512
CORONAL VI-SGE	Head	COR	3D	GE	3.3 ms Flip angle 15°	10-15 ms	16 cm	1 mm	256x205

Fig. 1 A recommended pituitary MRI protocol to be adopted in patients with clinical and biochemical findings suspicious for an ACTH-secreting pituitary adenoma. These parameters should be maintained in post-contrast medium acquisitions. *cm* centimetres, *COR* coronal, *FOV* field of view, *FS* fat saturated post gadolinium, *GE* gradient echo, *ms* milliseconds, *SAG* sagittal, *SE* spin echo, *TE* echo time, *TR* repetition time, *VI-SGE* volume interpolated-spoiled gradient echo sequence

BIPSS

- **Sensitivity 88-100%**
- **Specificity 70-100%**
- **Lateralization 70%**



NEUROSURGICAL FOCUS

Neurosurg Focus 38 (2):E5, 2015

The role of inferior petrosal sinus sampling in ACTH-dependent Cushing's syndrome: review and joint opinion statement by members of the Italian Society for Endocrinology, Italian Society for Neurosurgery, and Italian Society for Neuroradiology

Francesca Pecori Giraldi, MD,[1,2] Luigi Maria Cavallo, MD, PhD,[3] Fabio Tortora, MD, PhD,[4] Rosario Pivonello, MD, PhD,[6] Annamaria Colao, MD, PhD,[6] Paolo Cappabianca, MD,[3] and Franco Mantero, MD, PhD,[5] on behalf of the Altogether to Beat Cushing's Syndrome Group

[1]Department of Clinical Sciences and Community Health, University of Milan; [2]Neuroendocrine Research Laboratory, Istituto Auxologico Italiano, Milan; [3]Division of Neurosurgery, Department of Neurosciences and Reproductive and Odontostomatological Sciences, and [6]Department of Clinical Medicine and Surgery, University of Naples Federico II; [4]Department of Neuroradiology, "Magrassi Lanzara" Clinical-Surgical Department, Second University of Naples, Naples; and [5]Endocrinology Unit, Department of Medicine, University of Padua, Italy

In the management of adrenocorticotropic hormone (ACTH)–dependent Cushing's syndrome, inferior petrosal sinus sampling (IPSS) provides information for the endocrinologist, the neurosurgeon, and the neuroradiologist. To the endocrinologist who performs the etiological diagnosis, results of IPSS confirm or exclude the diagnosis of Cushing's disease with 80%–100% sensitivity and over 95% specificity. Baseline central-peripheral gradients have suboptimal accuracy, and stimulation with corticotropin-releasing hormone (CRH), possibly desmopressin, has to be performed. The rationale for the use of IPSS in this context depends on other diagnostic means, taking availability of CRH and reliability of dynamic testing and pituitary imaging into account. As regards the other specialists, the neuroradiologist may collate results of IPSS with findings at imaging, while IPSS may prove useful to the neurosurgeon to chart a surgical course. The present review illustrates the current standpoint of these 3 specialists on the role of IPSS.

http://thejns.org/doi/abs/10.3171/2014.11.FOCUS14766

KEY WORDS inferior petrosal sinus sampling; Cushing's disease; Cushing's syndrome; diagnosis; pituitary adenoma; pituitary surgery; pituitary imaging

J Clin Endocrinol Metab, September 2015, 100(9):3231–3244

Conventional and Nuclear Medicine Imaging in Ectopic Cushing's Syndrome: A Systematic Review

Andrea M. Isidori, Emilia Sbardella, Maria Chiara Zatelli, Mara Boschetti, Giovanni Vitale, Annamaria Colao, and Rosario Pivonello, on behalf of the ABC Study Group*

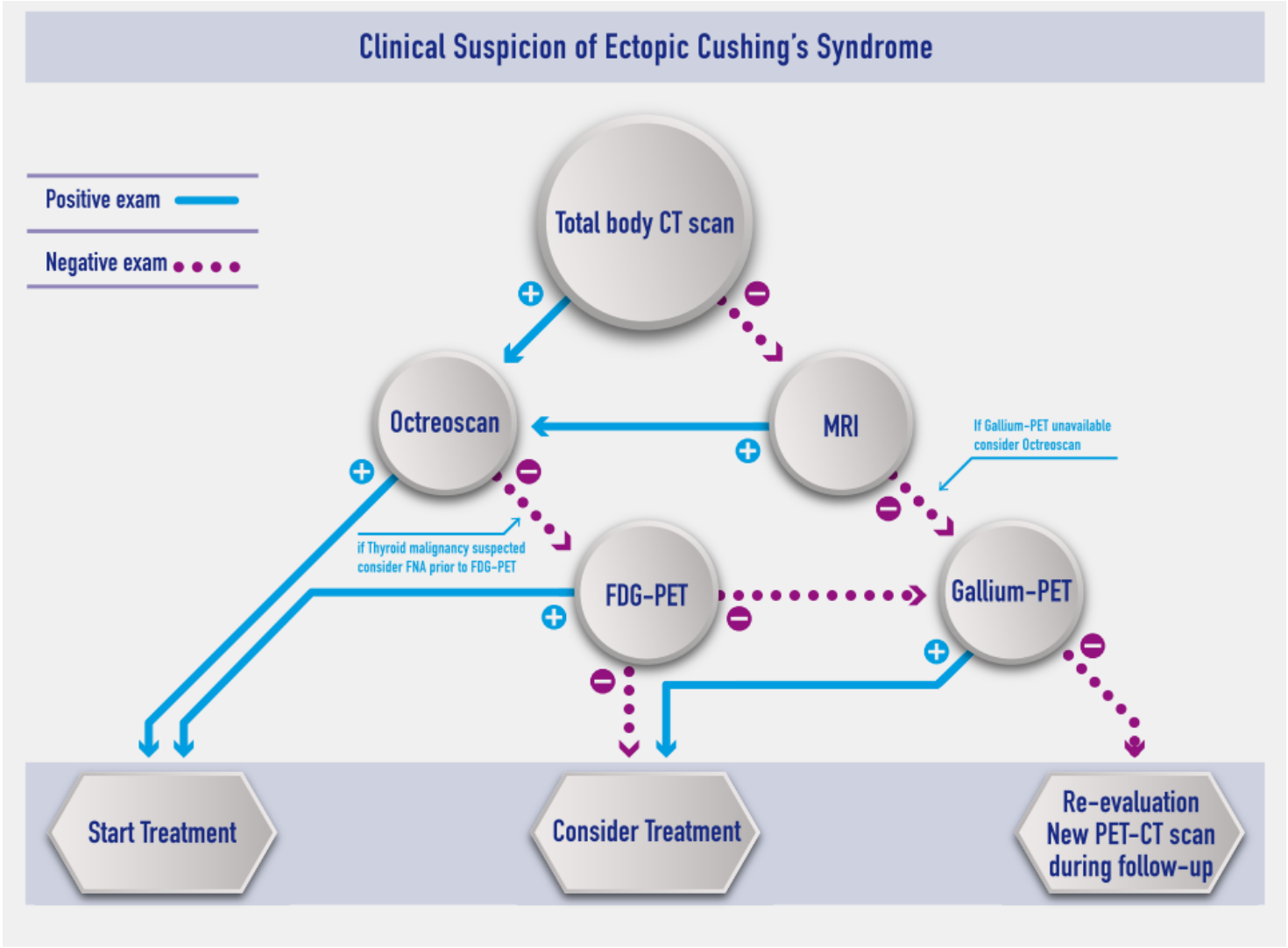


Figure 1. Clinical suspicion of ectopic CS.