Altogether to Beat Cushing's Syndrome

VIAGGIO ALLA (RI)SCOPERTA DELLA SINDROME DI CUSHING

Capri \ 15-18 maggio 2013
Certosa di San Giacomo
Hotel della Piccola Marina

Cause di sindrome di Cushing (e relativa prevalenza)

ACTH dipendente

- Malattia di Cushing 65 – 70 %
- Secrezione ectopica di ACTH da parte di tumori non ipofisari 10-15%
- Secrezione ectopica di CRH da parte di tumori non ipotalamici che induce ipersecrezione ipofisaria di ACTH < 1 %
- Sindrome di Cushing iatrogena o factizia da somministrazione di ACTH esogeno < 1%

ACTH indipendente

- Sindrome di Cushing iatrogena o factizia (la forma piu comune)
- Adenoma e carcinoma surrenalico 18 – 20%
- Iperplasia bilaterale micronodulare (PPNAD)Primary pigmented nodular adrenocortical disease < 1%
- Iperplasia surrenalica bilaterale macronodulare ACTH indipendente < 1%

Pituitary ACTH Dependency of Nodular Adrenal Hyperplasia in Cushing's Syndrome

Report of Two Cases and Review of the Literature

DAVID C. ARON, M.D.*
JAMES W. FINDLING, M.D.
PAUL A. FITZGERALD, M.D.
ROBERT M. BROOKS, M.D.
FRANK E. FISHER, M.D.†
PETER H. FORSHAM, M.D.
J. BLAKE TYRRELL, M.D.
San Francisco, California

Cushing's syndrome due to nodular adrenal hyperplasia comprises a clinically and biochemically heterogeneous group of disorders whose pathogenesis is unclear. We describe two patients with atypical steroid dynamics and large unilateral adrenal nodules who had pituitary ACTH-dependent disease. In the differential diagnosis of Cushing's syndrome, we recommend repeated ACTH measurement and selective venous sampling—particularly in those patients with impaired dexamethasone suppressibility and abnormal findings on computerized tomography.

ACTH non soppresso

Incremento della concentrazione di ACTH dopo bisurrenectomia

Efficacia di forme di terapia dirette all'ipofisi

Evidenza di tumore ipofisario prima o dopo bisurrenectomia

Macronodular Adrenocortical Hyperplasia in Longstanding Cushing's Disease*

13 pazienti con iperplasia surrenalica macronodulare vs 18 pazienti con iperplasia «diffusa» o «micronodulare»

Età più avanzata
Durata di malattia superiore
Concentrazione di cortisolo e di ACTH simile (nel 40% dei casi ACTH superiore alla norma)
Minore soppressibilità dopo desametasone (significativa per alta dose dexa)
Minore sensibilità alla stimolazione con ACTH
Responsività a Metopirone
Responsività a CRH in uno/due pz testati vs due/due con iperplasia diffusa

Entità distinta dalla classica forma
Possibile forma di transizione

Smals 1984

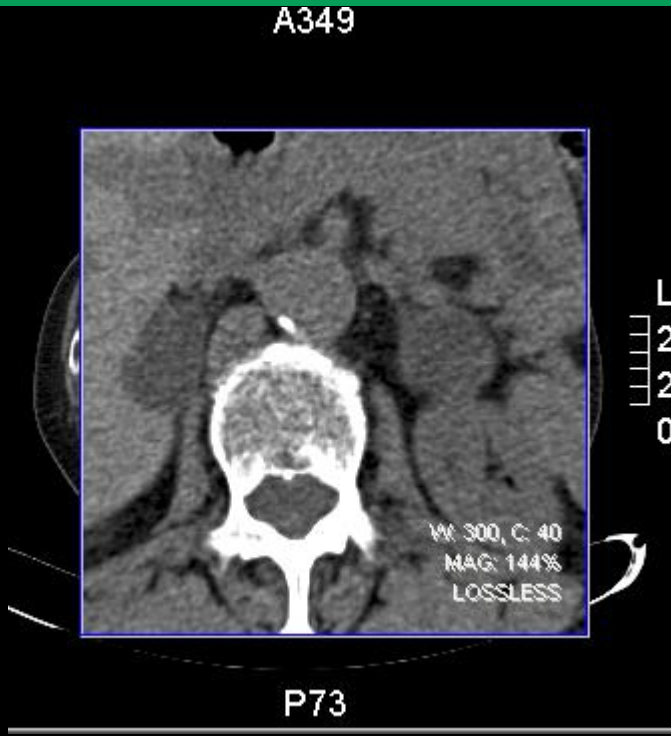
donna di 67 anni
necrosi asettica testa femore
nel passato sospetto di artropatia psoriasica,
di fibromialgia non confermate
osteoporosi con crolli vertebrali multipli
depressione in trattamento

⇩

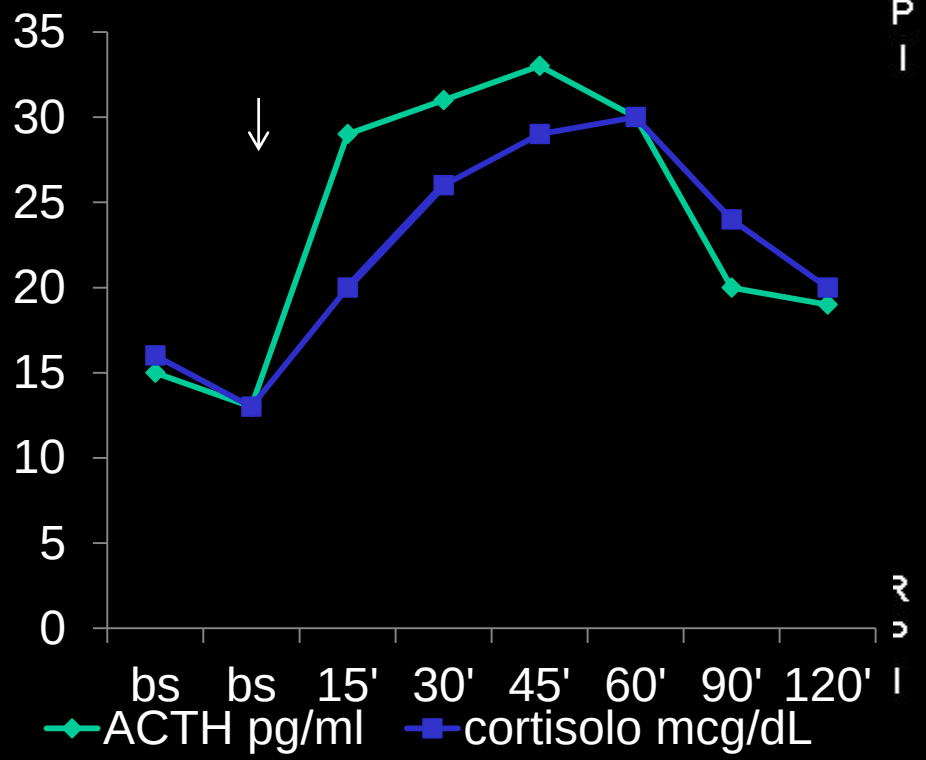
Sospetta origine secondaria di osteoporosi

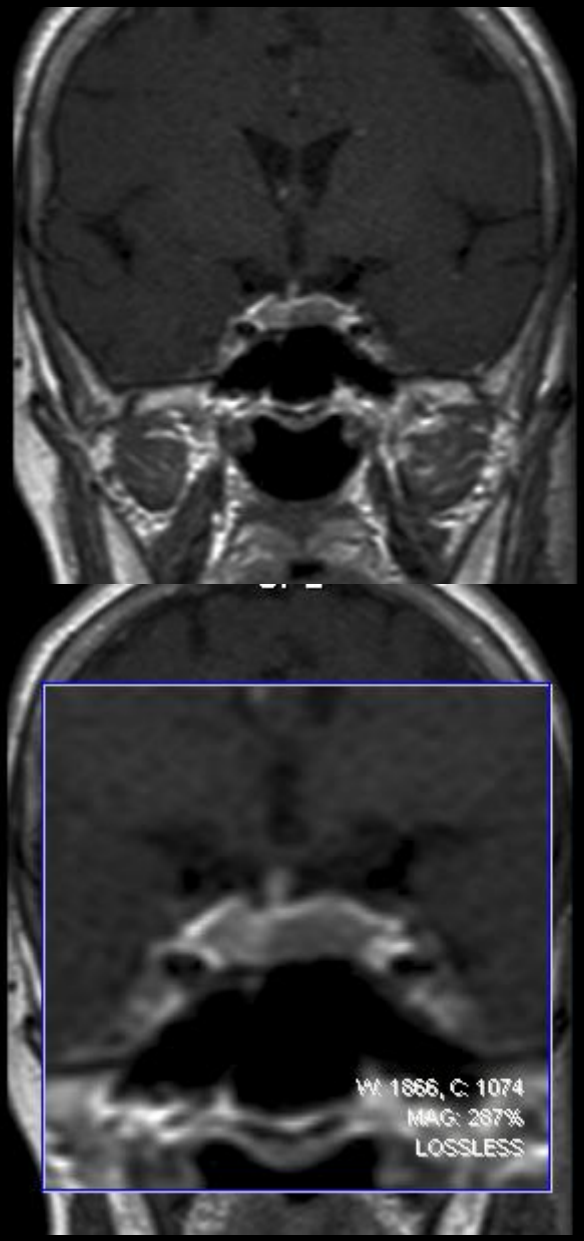
⇩

CLU 186-249 mcg/24h (vn fino a 137)
ritmo circadiano di F abolito
F dopo DEXA 1 mg 3,2 mcg/dL
ACTH 15 pg/ml

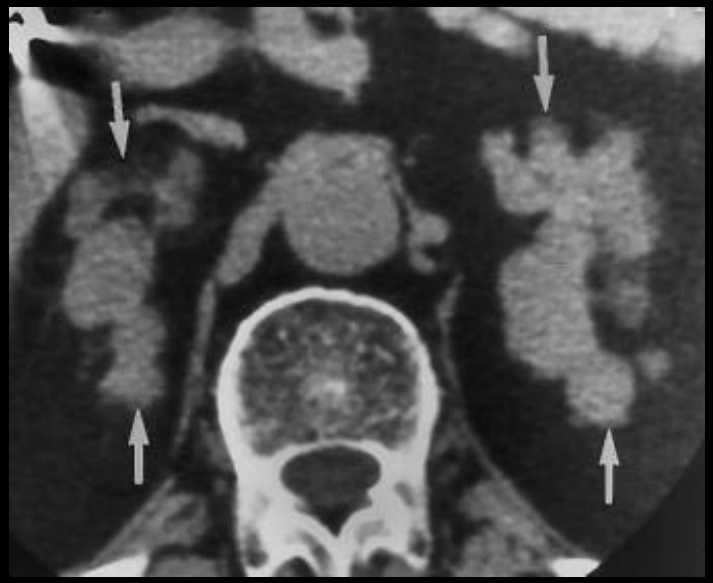


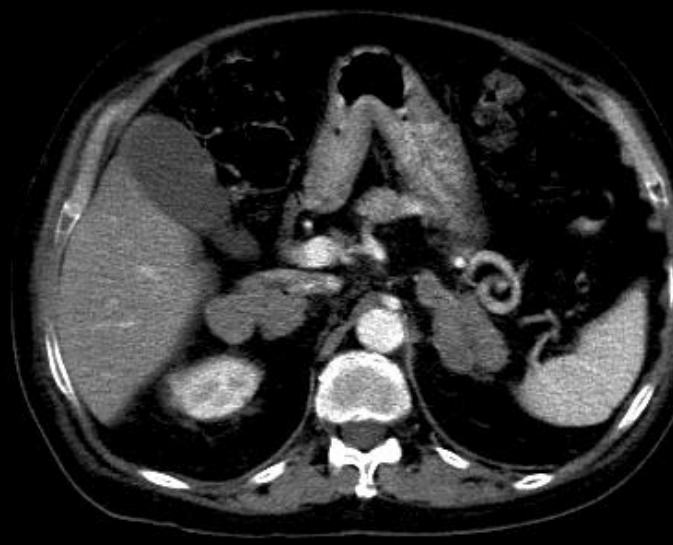
CRH 100 mcg ev





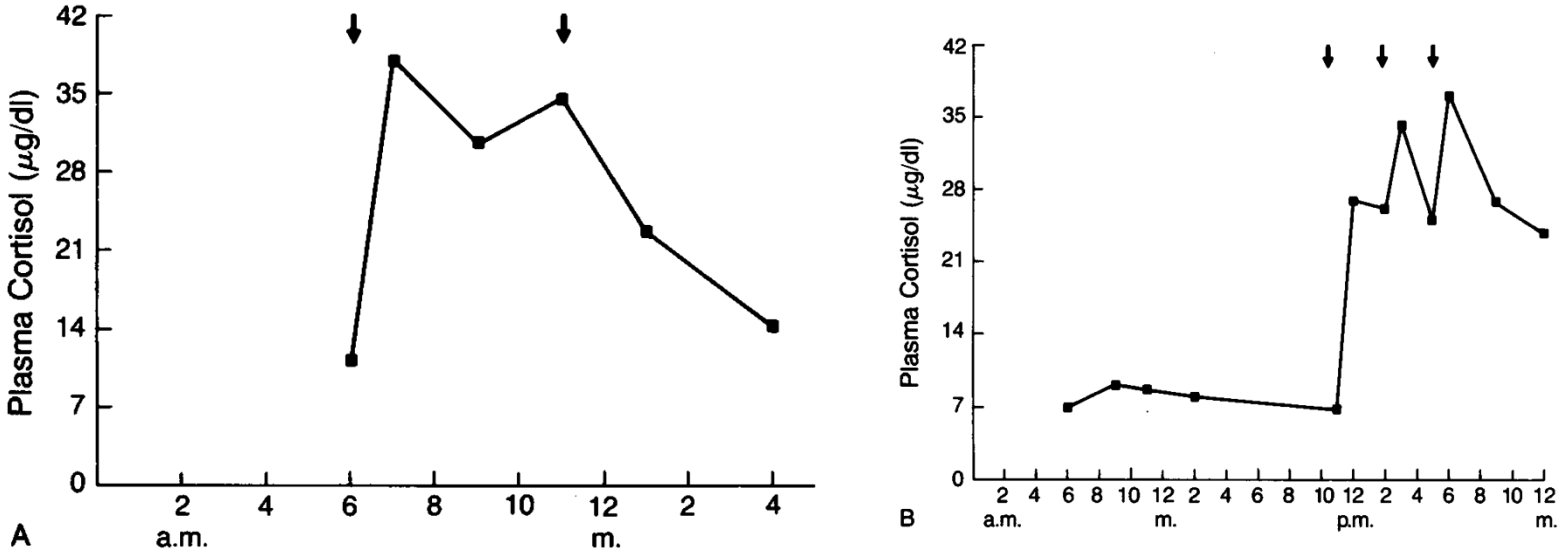
Iperplasia surrenalica macronodulare ACTH indipendente (AIMAH)





- donne di circa 50 anni
- malattia databile da anni, ma non devastante
- valori di cortisoluria elevati ma non molto
- concentrazione di ACTH non rilevabile e non stimolabile (da metopirone o vasopressina (Reznik) o da CRH (Lacroix) neppure nei seni petrosi inferiori
- nessuna soppressione di cortisolo plasmatico o urinario con dose bassa o alta di desametasone
- normalità dei rilevi radiologici a livello ipofisario
- captazione scintigrafica bilaterale di iodocolesterolo
- massivo ingrossamento dei surreni con macronoduli multip

GASTRIC INHIBITORY POLYPEPTIDE–DEPENDENT CORTISOL HYPERSECRETION — A NEW CAUSE OF CUSHING'S SYNDROME

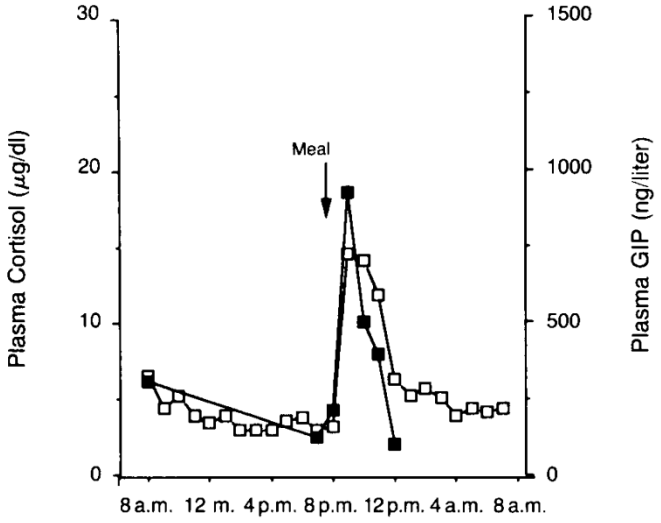


Plasma cortisol concentrations in a patient with food induced Cushing's syndrome during fasting and after eating. Cortisol concentrations measured in relation to meals (arrows) during the first and second day of oral high-dose dexamethasone testing

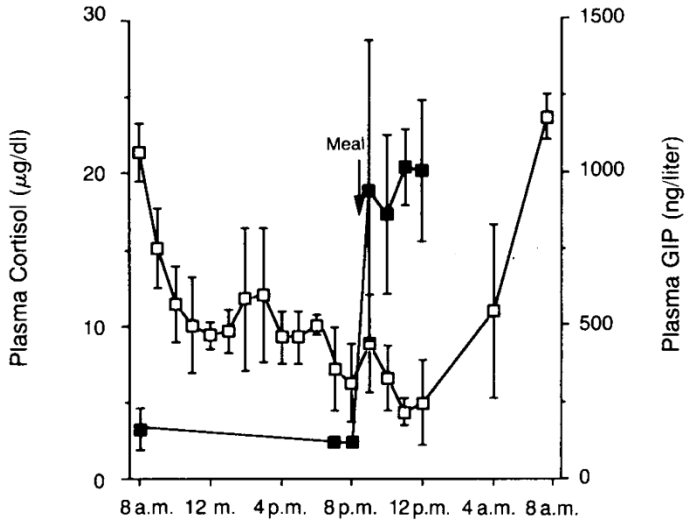
Lacroix 1992

FOOD-DEPENDENT CUSHING'S SYNDROME MEDIATED BY ABERRANT ADRENAL SENSITIVITY TO GASTRIC INHIBITORY POLYPEPTIDE

patient

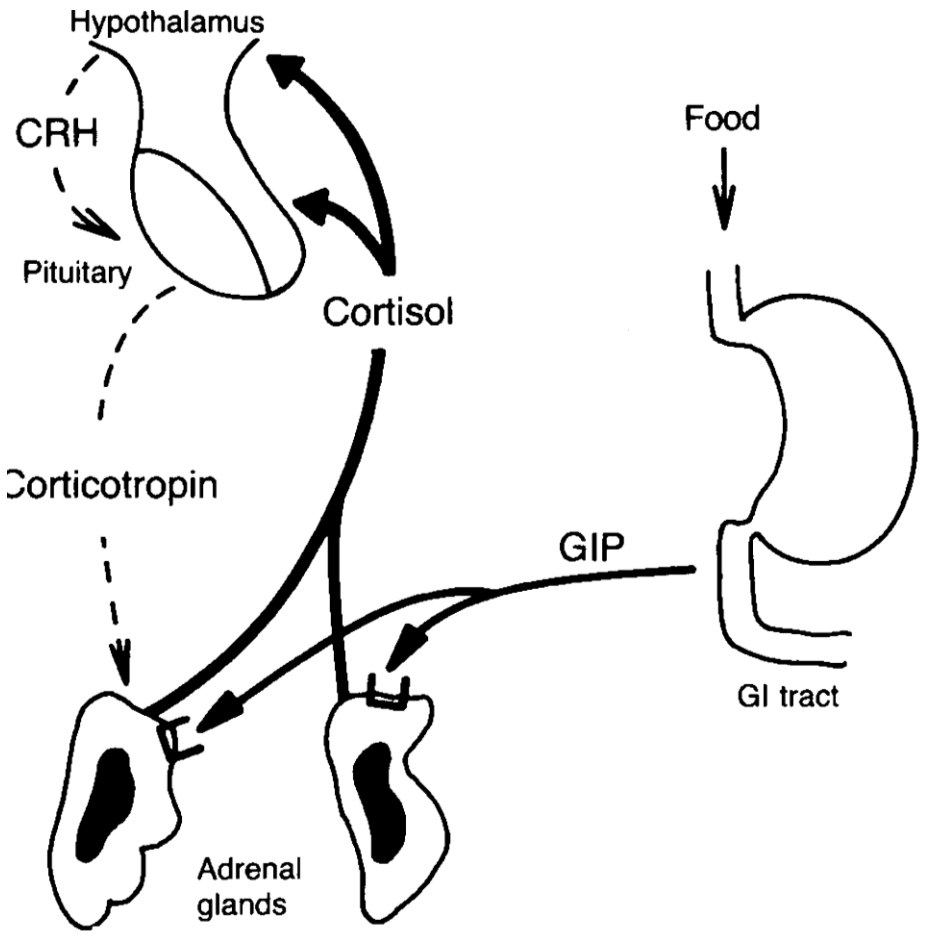


normal men



The 24 hour profile of plasma cortisol (white) and GIP (black) concentrations in a patient with food dependent Cushing's syndrome and three normal men

Reznik 1992



Lacroix 1992

Clinical and Genetic Heterogeneity, Overlap with Other Tumor Syndromes, and Atypical Glucocorticoid Hormone Secretion in Adrenocorticotropin-Independent Macronodular Adrenal Hyperplasia Compared with Other Adrenocortical Tumors

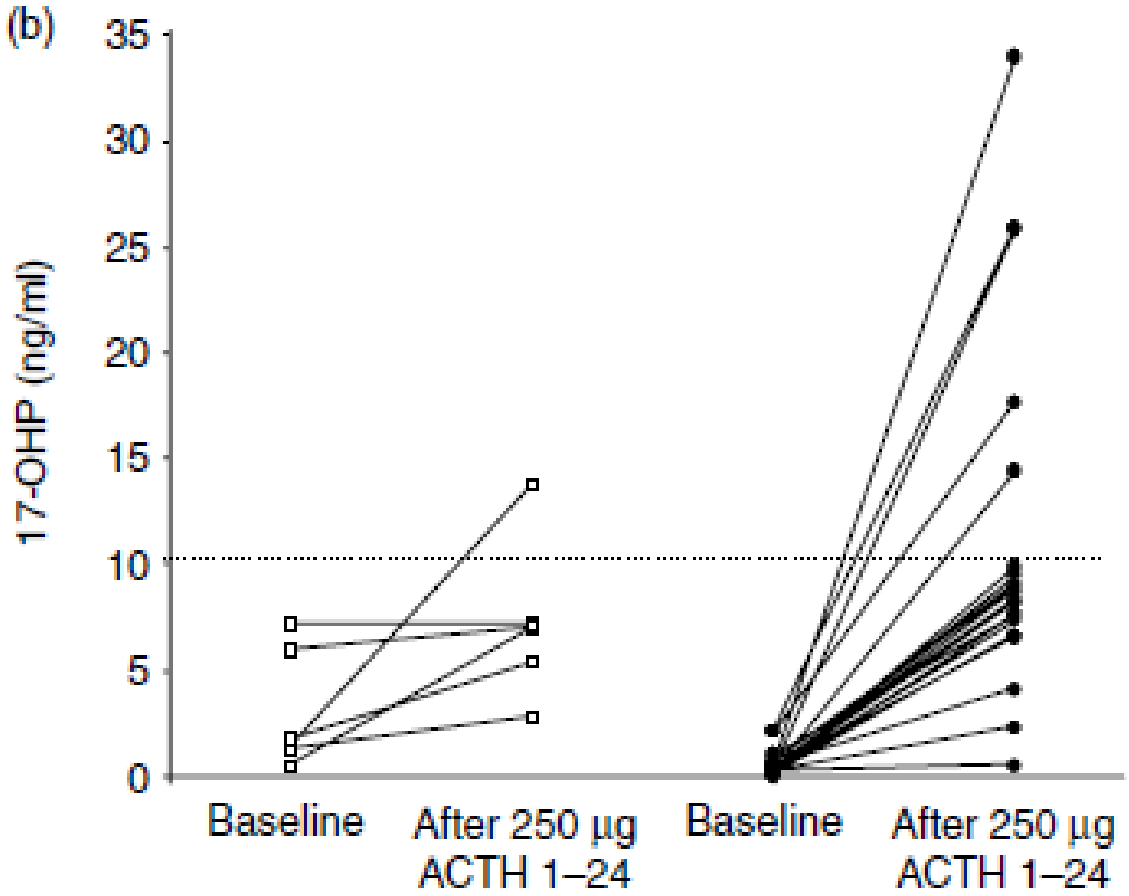
TABLE 1. Clinical and laboratory data for all patients with ACTH-independent macronodular adrenal hyperplasia and other adrenocortical tumors

	AIMAH (n = 16)	ACS (n = 15)	APA (n = 19)	SCA (n = 32)	*P* value
Gender (F:M)	11:5	11:4	7:12	25:7	
Age (yr)	46.8 ± 9.8	44.3 ± 14.8	51.2 ± 10.0	49.0 ± 10.7	0.32
8 AM cortisol (nmol/liter)	535.2 ± 198.6[a]	538.0 ± 215.2[a]	433.2 ± 82.8	389.0 ± 140.7	0.03
12 midnight cortisol (nmol/liter)	435.9 ± 242.8[b,c]	471.8 ± 355.9[b,c]	168.3 ± 57.9	129.7 ± 69.0	<0.01
ACTH (pmol/liter)	1.9 ± 2.5[b]	0.7 ± 0.4[d]	4.8 ± 3.7	3.5 ± 2.3	<0.01
Cortisol, before DEX (nmol/liter)	527.0 ± 157.3	405.6 ± 126.9	485.6 ± 209.7	449.7 ± 182.1	0.35
Cortisol, after DEX (nmol/liter)	320.0 ± 298.0[a,b]	303.5 ± 223.5[a]	93.8 ± 88.3	85.5 ± 60.7	<0.01
UFC (nmol/d · g creatinine)	611.9 ± 320.7[c,d]	625.7 ± 448.5[c,d]	183.5 ± 123.6	135.2 ± 64.0	<0.01
17OHS (mmol/d · g creatinine)	43.1 ± 20.4[c,d]	29.8 ± 13.8[b]	15.2 ± 10.8	18.2 ± 12.7	<0.01
Change at d 6 in Liddle's test (%)					
UFC	18.0 ± 48.0[b,c]	44.6 ± 109.7[b,c]	−98.7 ± 0.1	−90.3 ± 15.6	<0.01
17OHS	14.2 ± 47.1[b,c]	10.6 ± 44.9[a]	−61.2 ± 7.5	−57.5 ± 18.8	<0.01

a P 0.05 compared with SCA.
b P 0.05 compared with APA.
c P 0.01 compared with SCA.
d P 0.01 compared with APA.

Hsiao 2009

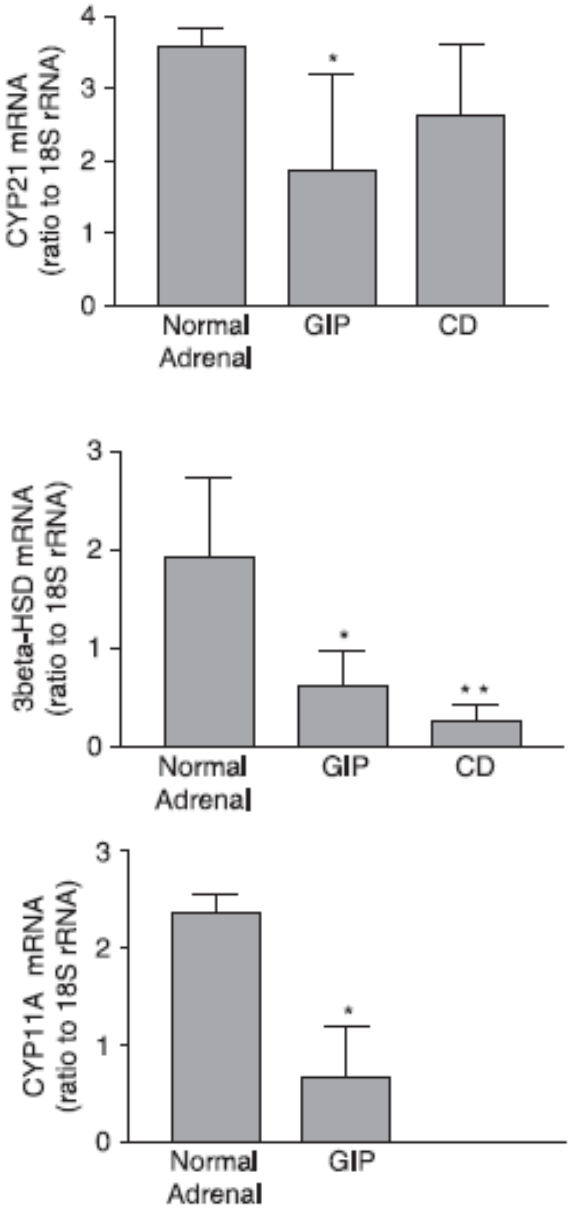
Aberrant cortisol regulations in bilateral macronodular adrenal hyperplasia: a frequent finding in a prospective study of 32 patients with overt or subclinical Cushing's syndrome



Response of serum 17-OHP after the administration of 250 mg ACTH in patients with CS (white boxes) and with SCS (black dots)

Libè 2010

Expression of ACTH receptor pathway genes in glucose-dependent insulinotrophic peptide (GIP)-dependent Cushing's syndrome



Expression levels of CYP11A, 3β-HSD and CYP21 mRNA (CYP11A/r18S, 3β-HSD/r18S and CYP21/r18S ratios) in normal adrenals, GIP-dependent adrenal tissues, and adrenals from patients with CD. Each bar and line represents the mean ±SD of the ratio. *Significantly different from normal at $P < 0{\cdot}002$ for CYP21, $P < 0{\cdot}04$ for 3β-HSD and $P < 0{\cdot}04$ for CYP11A. **Significantly different from normal at $P < 0{\cdot}06$ for 3β-HSD.

Antonini 2006

Caratteristiche suggestive di AIMAH

Età più avanzata che per altre forme di ipertisolismo ACTH indipendente

Frequente forma subclinica di ipercortisolismo (ACTH dosabile e responsivo a CRH)

Possibili concentrazioni ridotte di cortisolo a digiuno (ed elevate dopo il pasto)

Elevata risposta di 17OHP alla stimolazione con ACTH

Recettori ormonali «illeciti»

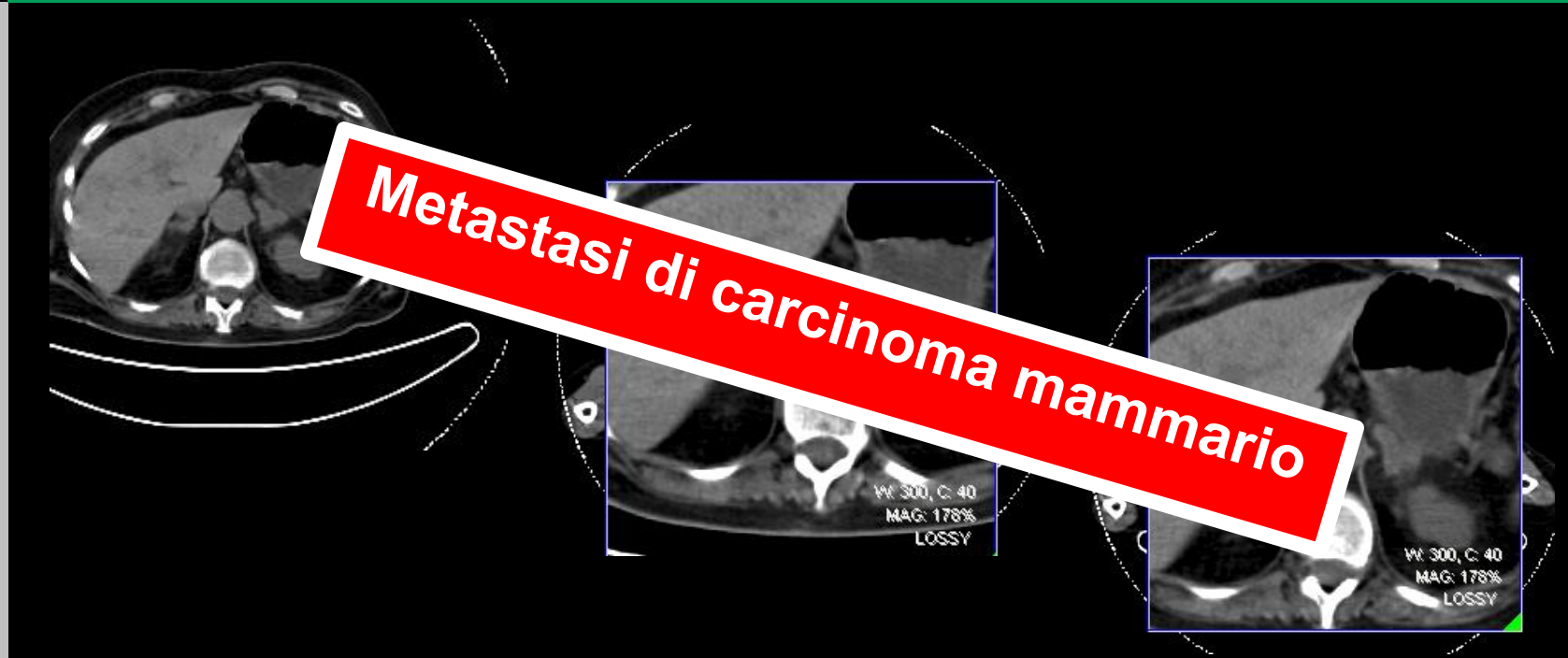
GIP
Vasopressina
Catecolamine
LH/hCG
Serotonina
Angiotensina

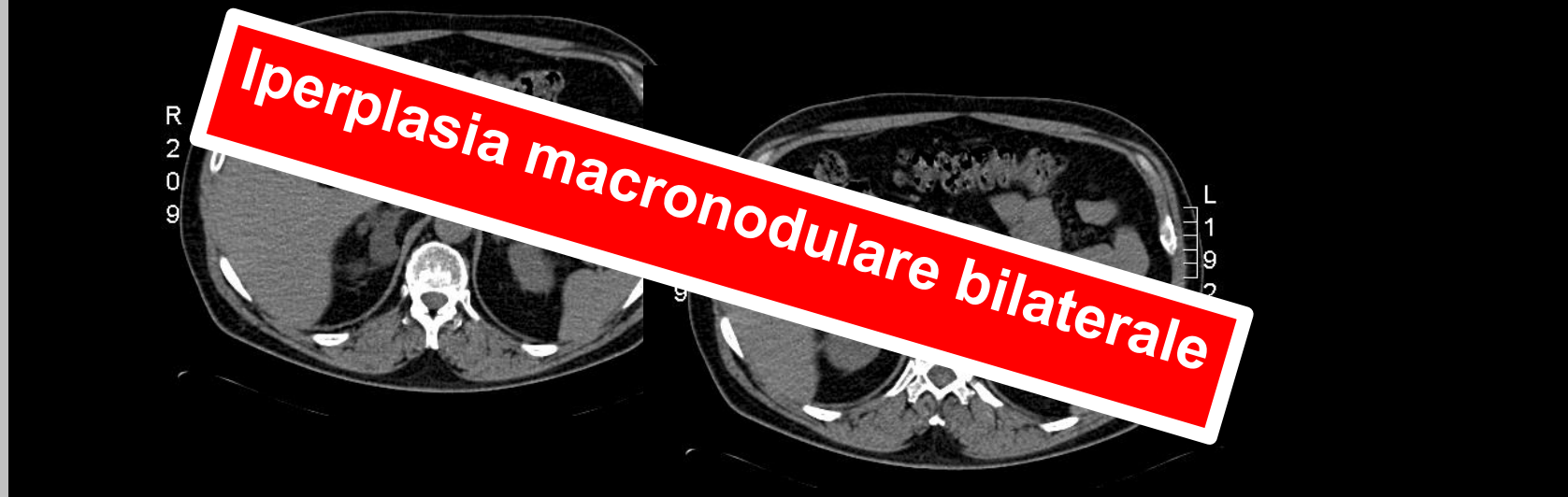
In vivo screening protocol to detect the presence of aberrant hormone receptors in adrenal Cushing's syndrome

Time, min	Day 1	Day 2	Day 3
-60	Fasting-supine	Fasting-supine	Fasting-supine
-15	*	*	*
0	Upright*	GnRH 100 mcg IV	Glucagon 1 mg IV*
+30'	Upright*	*	*
+60'	Upright*	*	*
+90'	Upright*	*	*
+120'	Upright*	*	*
+150'	Supine*	(Meal)	
+180'	Mixed meal*		Vasopressin 10 IU IM*
+210'	*		*
+240'	*		*
+270'	*	*	*
+300'	*	TRH 200 mcg IV	*
+330'		*	
+360'	ACTH 1-24 250mcg IV*	*	Metoclopramide 10 mg orally *
+390'	*	*	*
+420'	*	*	*
+450'	*		*
+480'	*		*

*Blood samples for determination of cortisol, ACTH, other hormones and vital signs

Lacroix 1999


Metastasi di carcinoma mammario
W: 300, C: 40
MAG: 178%
LOSSY
W: 300, C: 40
MAG: 178%
LOSSY


Iperplasia macronodulare bilaterale
R
2
0
9
L
1
9
2

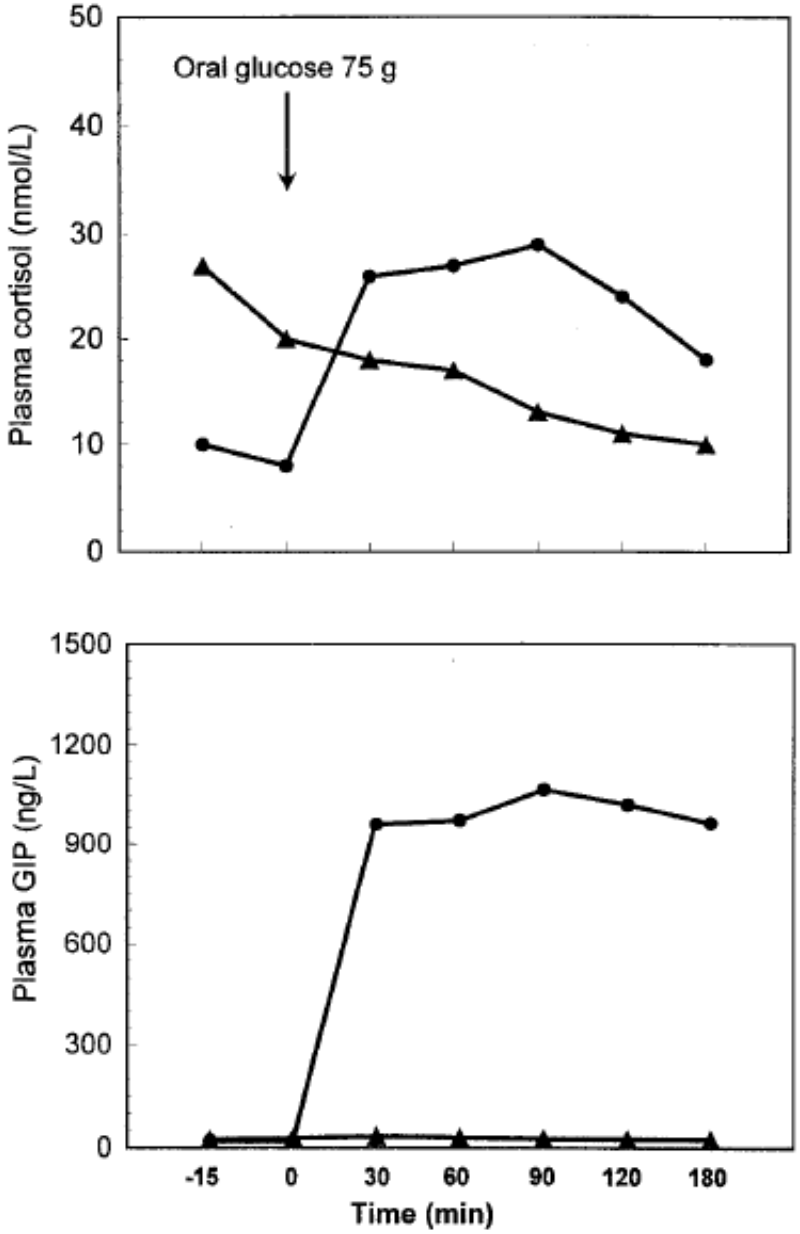
The Ectopic Expression of the Gastric Inhibitory Polypeptide Receptor Is Frequent in Adrenocorticotropin-Independent Bilateral Macronodular Adrenal Hyperplasia, but Rare in Unilateral Tumors

Prevalenza della espressione «ectopica» del recettore di GIP in 16 adenomi surrenalici, 14 carcinomi e 8 AIMAH:

1/ 16 AA
0/14 AC
4/8 AIMAH

Groussin 2002

Asynchronous Development of Bilateral Nodular Adrenal Hyperplasia in Gastric Inhibitory Polypeptide-Dependent Cushing's Syndrome

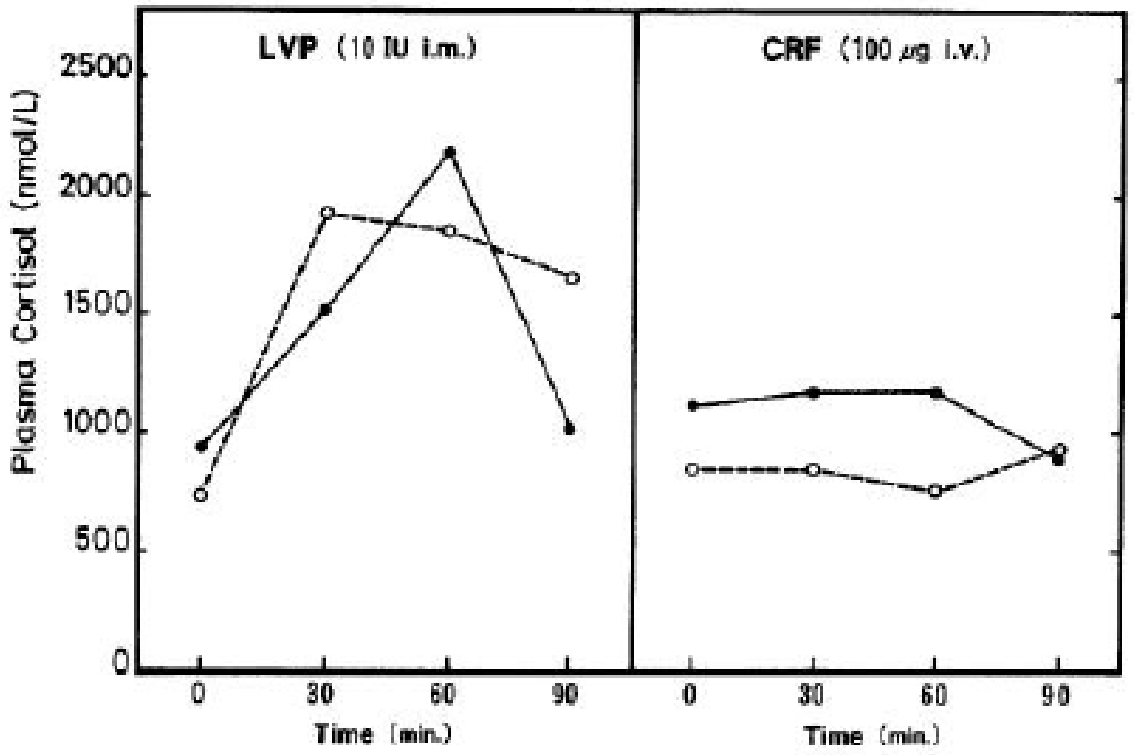


Plasma cortisol and GIP responses to 75 g oral glucose administration given 3 months after right adrenalectomy in the patient with GIP-dependent Cushing's syndrome. After the right adrenalectomy , Tests were performed on two different mornings, after a 12-h overnight fast either without (circle), or 60 min after the sc administration of 100mg Octreotide (triangle)

N'Diaye 1999

vasopressina

Lysine Vasopressin Stimulation of Cortisol Secretion in Patients with Adrenocorticotropin-Independent Macronodular Adrenal Hyperplasia

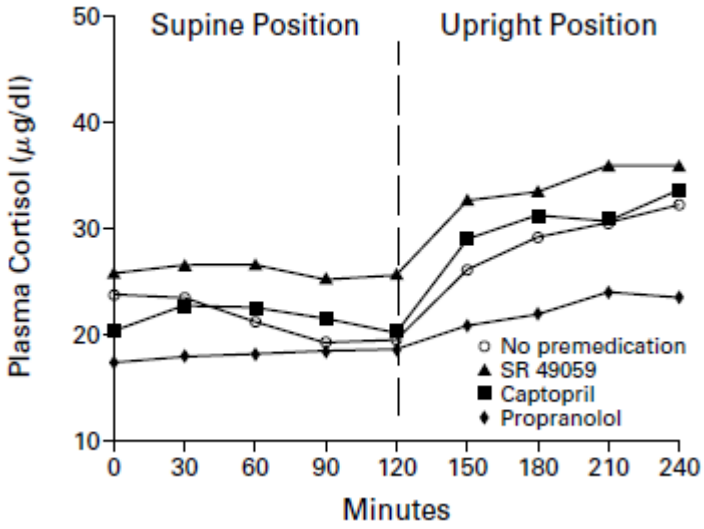


Plasma cortisol levels after LVP and hCRH injection in patient 1 and patient 2 . Both patients showed plasma cortisol responses to LVP (left panel), but not to hCRH (right panel). Plasma ACTH levels remained undetectable after both stimuli in the two patients.

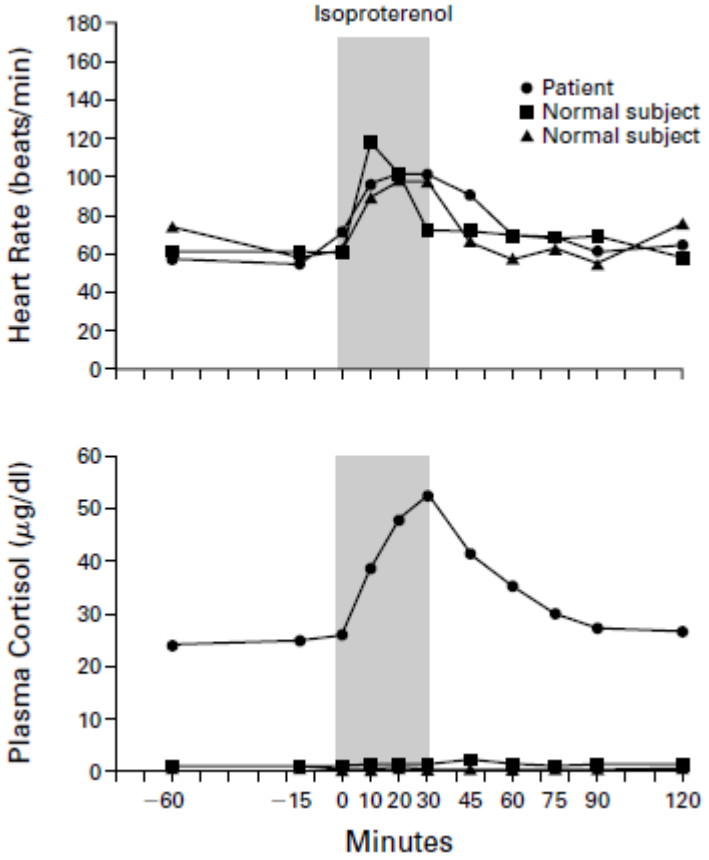
Horiba 1995

Recettore beta adrenergico

PROPRANOLOL THERAPY FOR ECTOPIC *b*-ADRENERGIC RECEPTORS IN ADRENAL CUSHING'S SYNDROME



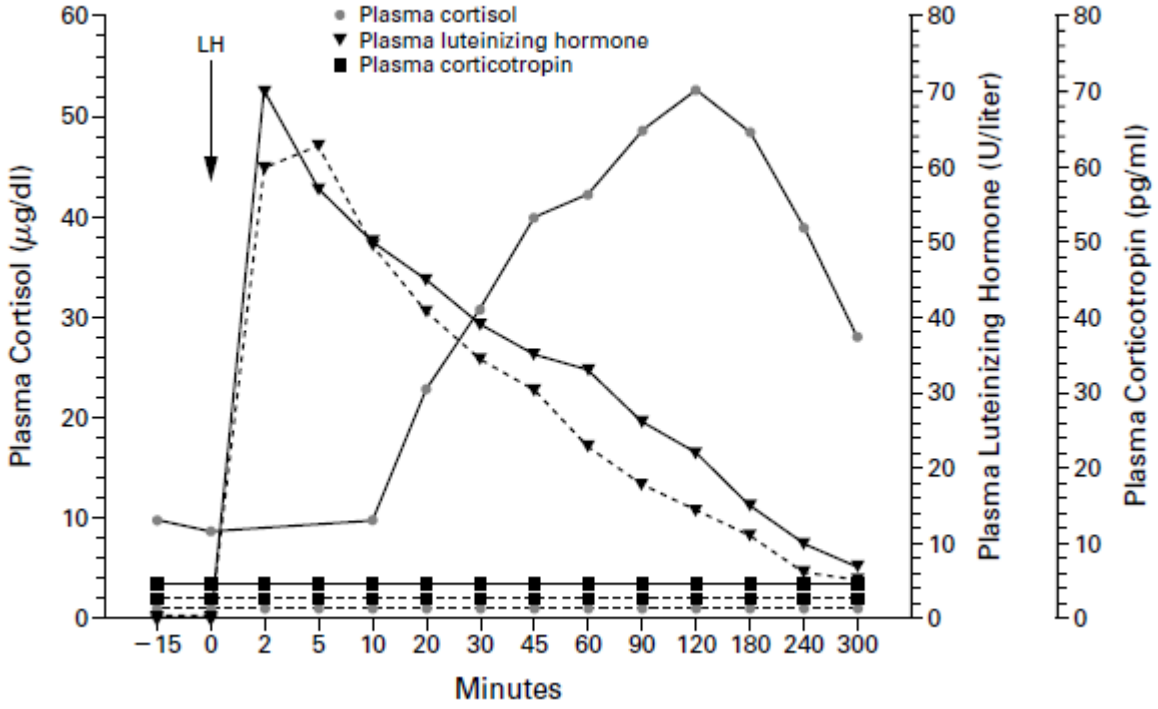
Effects of Posture on Plasma Cortisol Concentrations in a Patient with Cushing's Syndrome and Bilateral Macronodular Adrenal Hyperplasia.



Changes in the Heart Rate and Plasma Cortisol Concentrations during the Infusion of Isoproterenol in a Patient with Cushing's Syndrome and Corticotropin-Independent Bilateral Macronodular Adrenal Hyperplasia and Two Normal Subjects.

Lacroix 1997

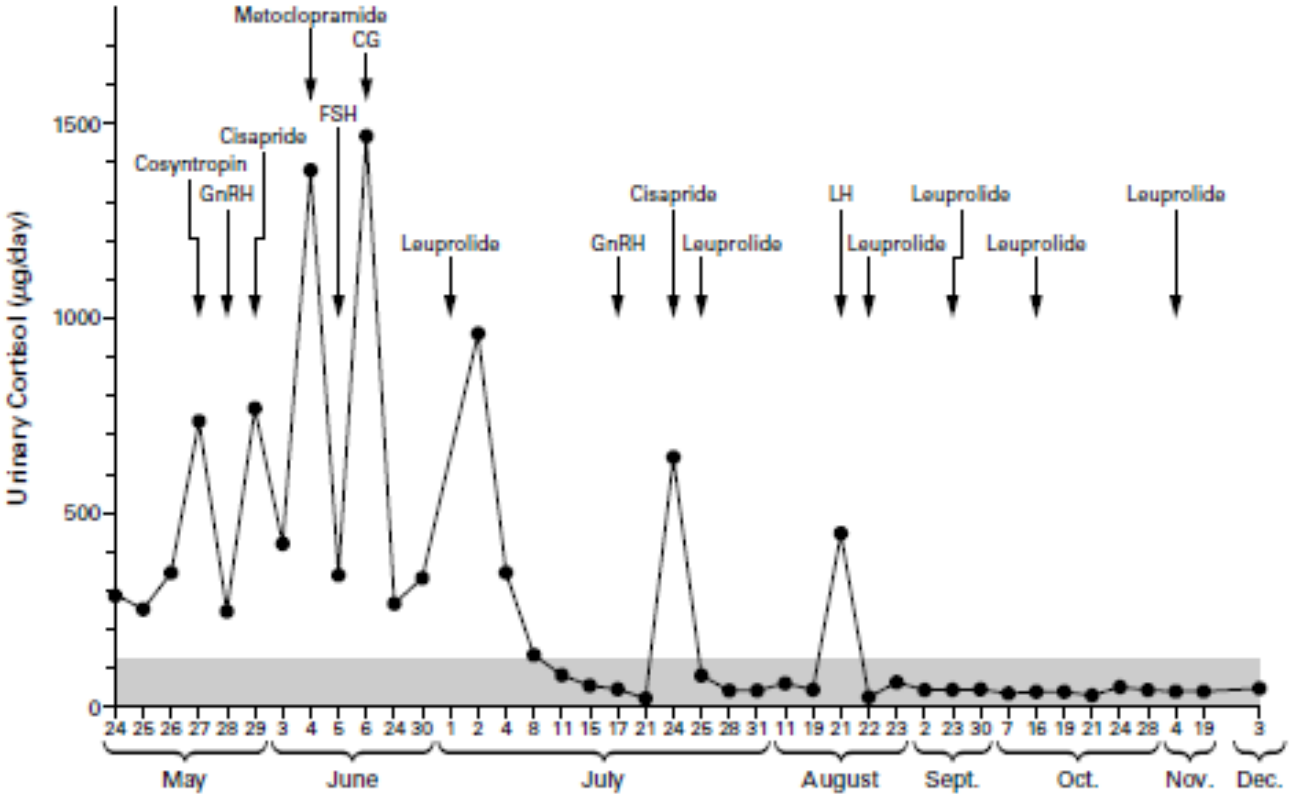
Leuprolide acetate therapy in Luteinizing hormone-dependent Cushing's syndrome



Plasma Cortisol, Luteinizing Hormone, and Corticotropin Concentrations after the Intravenous Administration of 300 U of Recombinant Human Luteinizing Hormone (LH; Arrow) in the Patient with Cushing's Syndrome and Corticotropin-Independent Bilateral Macronodular Adrenal Hyperplasia (Solid Lines) and a Control Woman (Dashed Lines).

Lacroix 1999

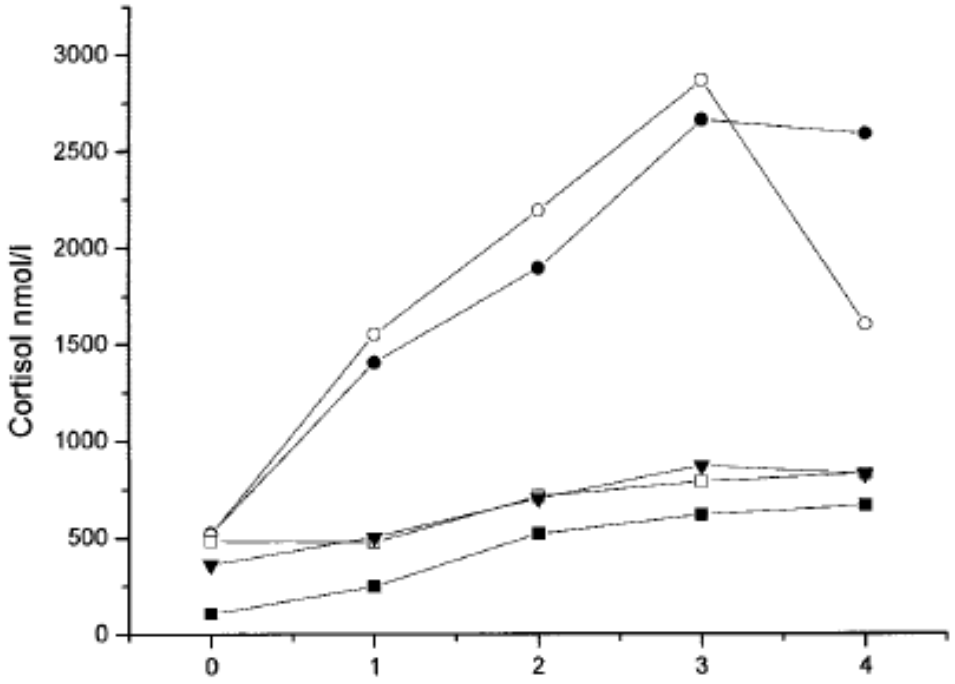
Leuprolide acetate therapy in Luteinizing hormone-dependent Cushing's syndrome



Urinary Cortisol Excretion in a Patient with Cushing's Syndrome and Bilateral Macronodular Adrenal Hyperplasia during Initial Studies and Treatment

Lacroix 1999

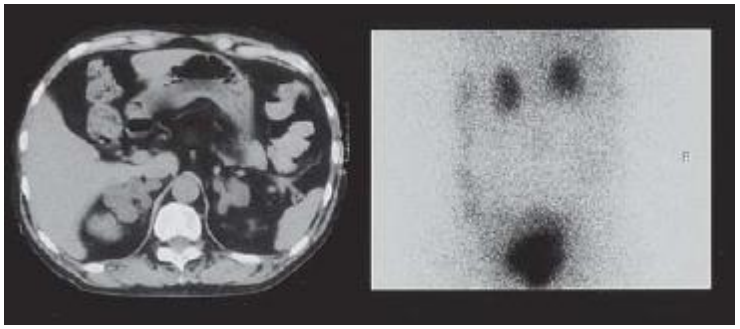
Cushing's Syndrome in a Patient with Bilateral Macronodular Adrenal Hyperplasia Responding to Cisapride: An in Vivo and in Vitro Study



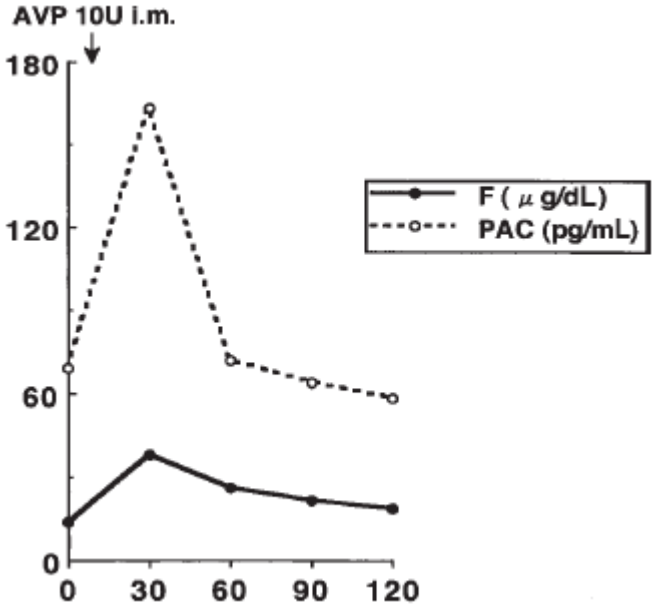
Cortisol response to cisapride administration (10 mg orally) before surgery (*filled circles*, first testing; *open circles*, second testing) and after surgery (*filled squares*, 1 wk after surgery; *open squares*, 4 months after surgery; *filled triangles*, 16 months after surgery).

Mannelli 2003

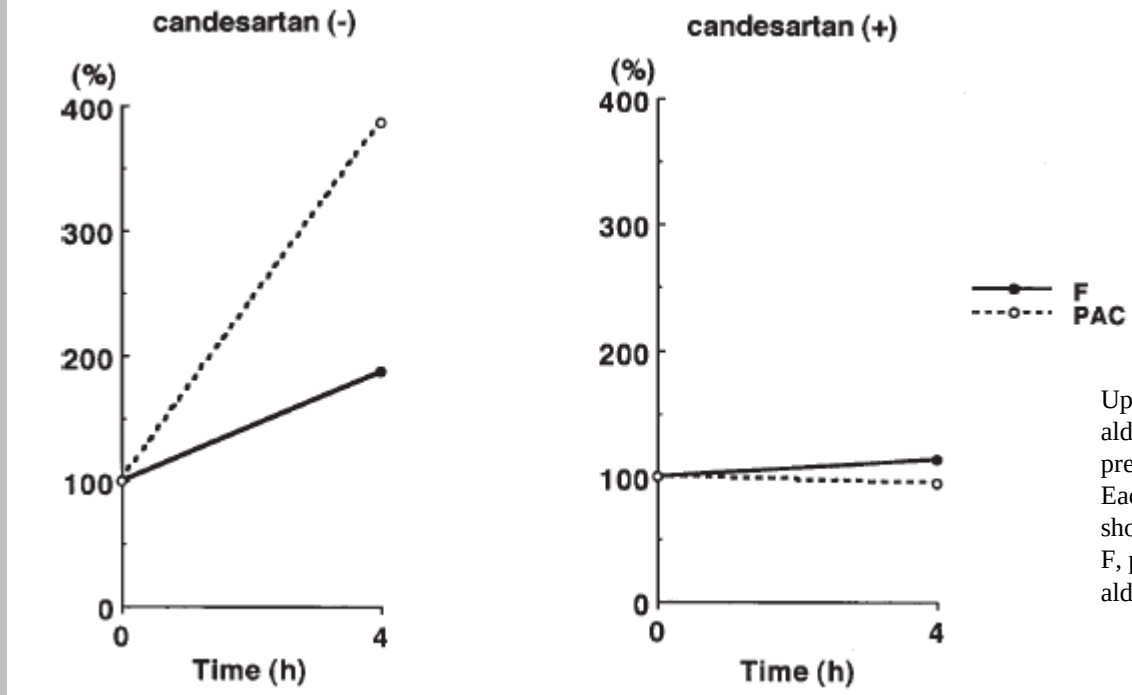
Case of ACTH–Independent Macronodular Adrenal Hyperplasia with Possible Adrenal Hypersensitivity to Angiotensin II



(Left) Abdominal CT of the patient demonstrating nodular enlargement of bilateral adrenal glands; **(right)** iodocholesterol scintigraphy while taking 2 mg of dexamethasone daily, which reveals a marked uptake of radioactivity into the bilateral adrenal glands.



AVP loading test (10 U intramuscularly). F, plasma cortisol concentration (μg/dL); PAC, plasma aldosterone concentration (pg/mL).



Upright posture (4 h) test. Changes in plasma cortisol and aldosterone levels without **(left)** or with **(right)** pretreatment with 8 mg of candesartan are demonstrated. Each hormone concentration after upright posture is shown as a percentage of baseline value.
F, plasma cortisol concentration; PAC, plasma aldosterone concentration

Nakamura 2001

Screening per recettori ormonali «illeciti»

The Ectopic Expression of the Gastric Inhibitory Polypeptide Receptor Is Frequent in Adrenocorticotropin-Independent Bilateral Macronodular Adrenal Hyperplasia, but Rare in Unilateral Tumors,
Groussin 2002

1/ 16 AA
0/14 AC
4/8 AIMAH

Clinical and Genetic Heterogeneity, Overlap with Other Tumor Syndromes, and Atypical Gluco corticoid Hormone Secretion in Adrenocorticotropin Independent Macronodular Adrenal Hyperplasia Compared with Other Adrenocortical Tumors
Hsiao 2009

TABLE 2. Response to testing for aberrant receptor expression in patients with AIMAH and ACS

	AIMAH (n = 14)	%	ACS (n = 12)	%
Posture	4/11	36.4	3/12	25.0
Meal	1/12	8.3	0/11	0.0
GnRH	1/6	16.7	0/8	0.0
TRH	1/3	33.3	1/8	12.5
GHRH	2/11	18.2	0/10	0.0
Glucagon	0/10	0.0	2/11	18.2
Vasopressin	5/11	45.5	4/10	40.0

The denominator stands for the number of patients being tested; the numerator stands for the number of patients with positive response (>150% increasing).

Are Ectopic or Abnormal Membrane Hormone Receptors Frequently Present in Adrenal Cushing's Syndrome?*
Mircescu 2000

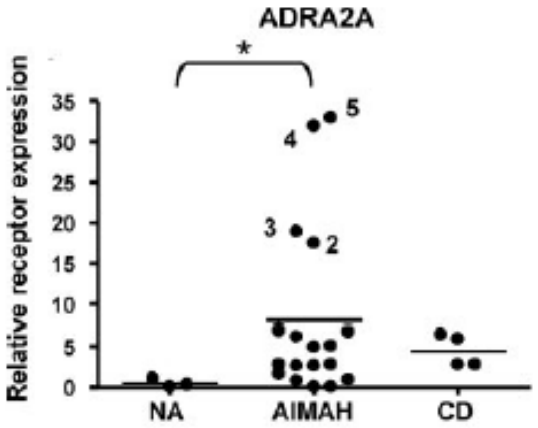
1/ 13 AA
0/1 AC
6/6 AIMAH

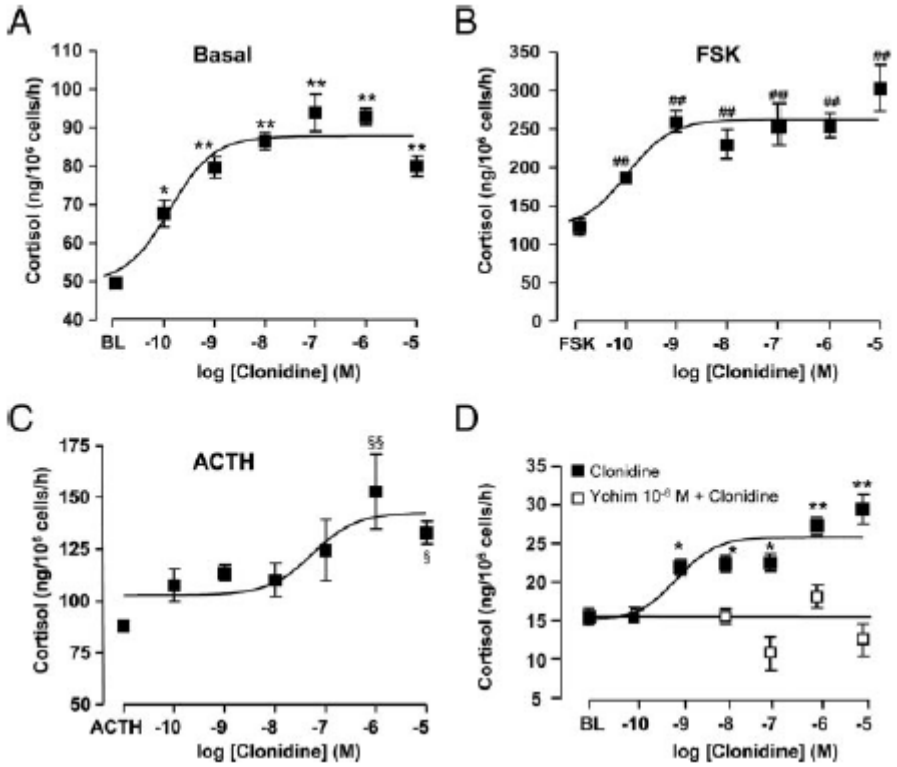
TABLE 2. Plasma cortisol responses to the various screening tests and associated abnormal hormone receptor in patients with AIMAH and Cushing's syndrome

Patient number	Upright posture	Mixed meal	GnRH (100 μg iv)	TRH (200 μg iv)	Glucagon (1 mg iv)	AVP (10 IU im)	Cisapride (10 mg orally)	Abnormal receptor
1	nd	398	nd	nd	106	66	nd	GIPR
2	143	61	89	89	82	337	nd	V1-AVPR
3	177	85	77	60	87	136	108	β-AR
4	169	57	89	74	89	247	128	V1-AVPR and β-AR
5	114	236	109	110	109	63	84	GIPR
6	106	81	214	62	81	91	476	LH/hCG and 5-HT_4

Cortisol values are expressed as percent maximal change from basal levels (100%). A value less than 125% was considered as a nonresponse, 125–149% as a partial response, and 150% and more as a positive response.
AIMAH, ACTH-independent macronodular hyperplasia; AVP, arginine-vasopressin; nd, not done.

Systematic Analysis of G Protein-Coupled Receptor Gene Expression in Adrenocorticotropin-Independent Macronodular Adrenocortical Hyperplasia Identifies Novel Targets for Pharmacological Control of Adrenal Cushing's Syndrome





Effect of graded concentrations (from 1010 to 105 M) of the ADRA2A agonist clonidine on basal and FSK- or ACTH-induced stimulation of cortisol production in AIMAH cells

Assie 2010

Cause molecolari implicate nella patogenesi di AIMAH

- **Gsα**
- **Menina**
- **MC2R**
- **APC**
- **FH**
- **PDE11A**

Terapia medica

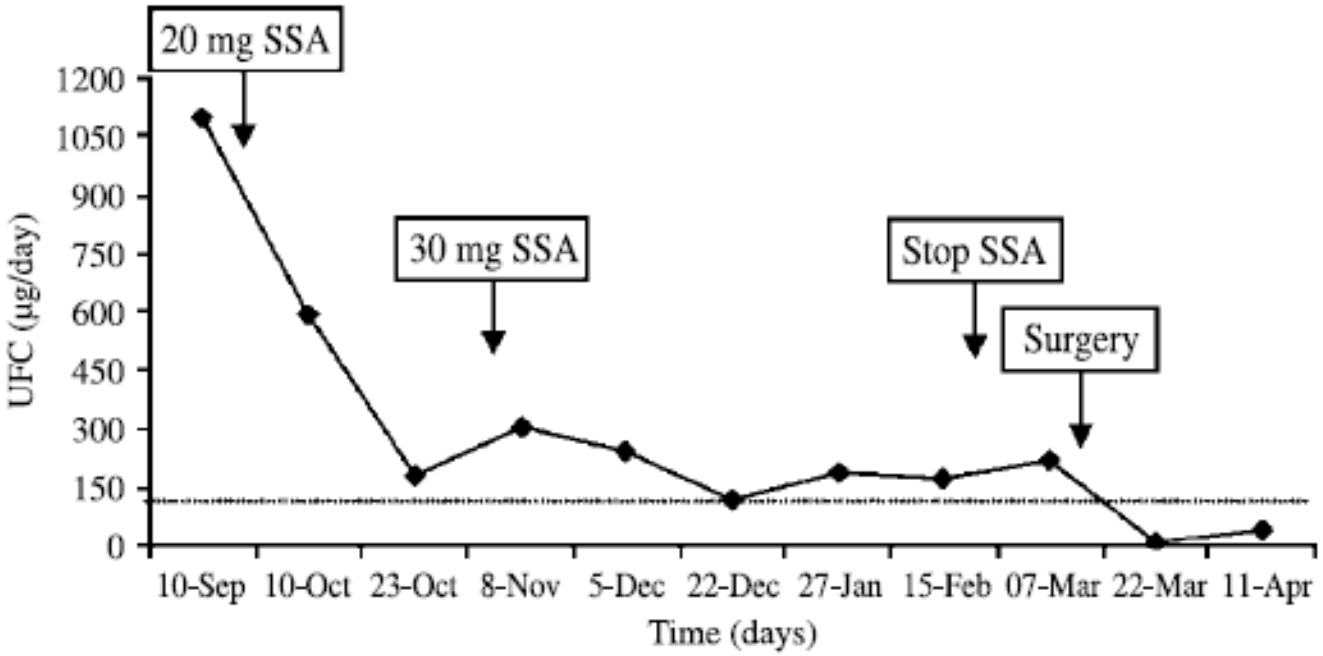
Analoghi di somatostatina

Antagonisti GnRH

Bloccanti beta-adrenergici

Inibitori steroidogenesi surrenalica

Food-dependent Cushing's syndrome: from molecular characterization to therapeutical results



Albiger 2007

Analoghi di somatostatina

FOOD-DEPENDENT CUSHING'S SYNDROME MEDIATED BY ABERRANT ADRENAL SENSITIVITY TO GASTRIC INHIBITORY POLYPEPTIDE

YVES REZNIK, M.D., VERONIQUE ALLALI-ZERAH, M.D., JEAN A. CHAYVIALLE, M.D., ROBERT LEROYER, PH.D., PIERRE LEYMARIE, M.D., GEORGES TRAVERT, PH.D., MARIE-CHRISTINE LEBRETHON, M.D., ILSE BUDI, M.D., ANNE-MARIE BALLIERE, M.D., AND JACQUES MAHOUDEAU, M.D.

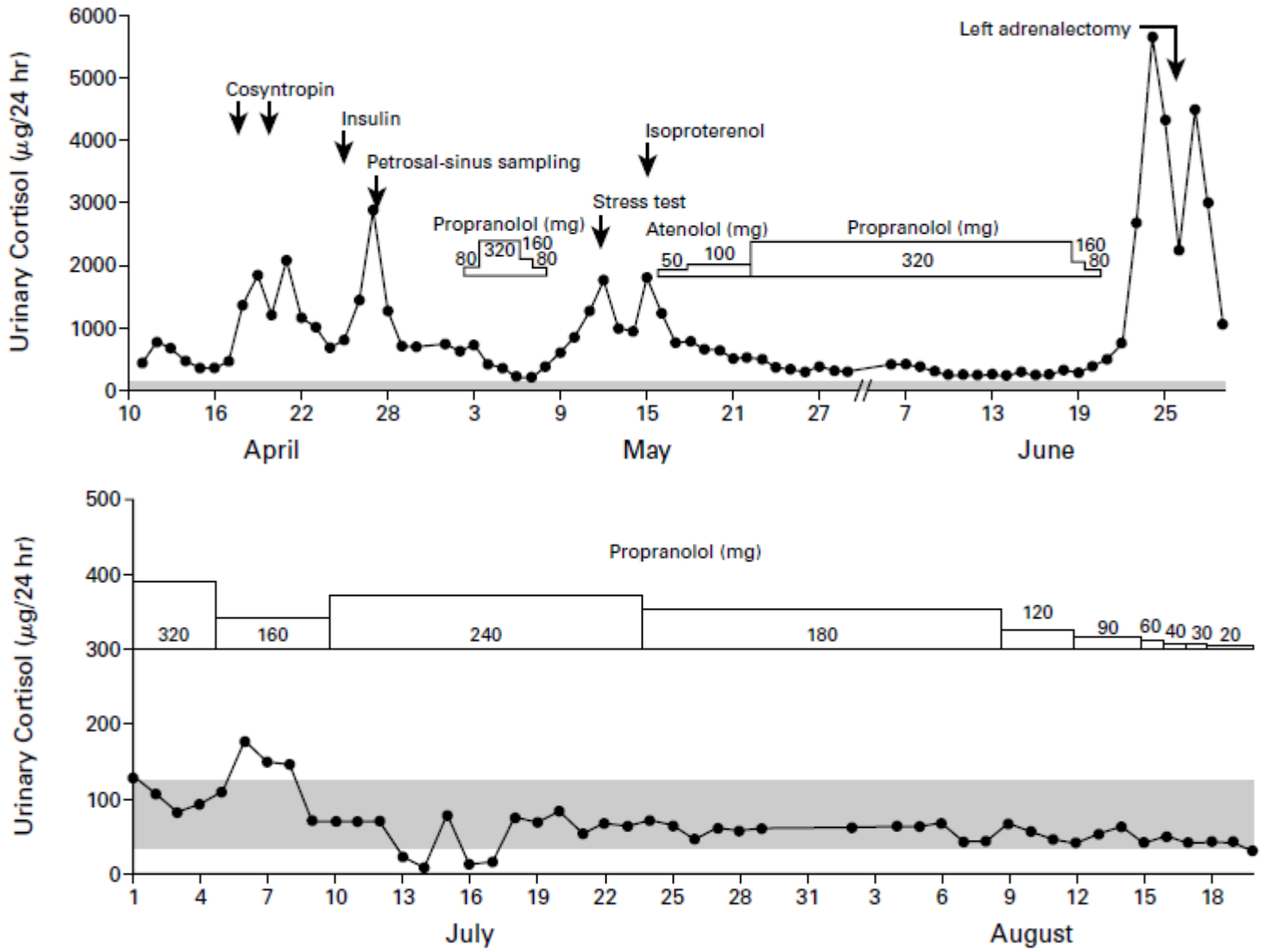
Food-Dependent Cushing's Syndrome Resulting from Abundant Expression of Gastric Inhibitory Polypeptide Receptors in Adrenal Adenoma Cells

WOUTER W. DE HERDER, LEO J. HOFLAND, TED B. USDIN, FRANK H. DE JONG, PIET UITTERLINDEN, PETER VAN KOETSVELD, ÉVA MEZEY, TOM I. BONNER, H. JAAP BONJER, AND STEVEN W. J. LAMBERTS

Transient Efficacy of Octreotide and Pasireotide (SOM230) Treatment in GIP-dependent Cushing's Syndrome

Preumont 2011

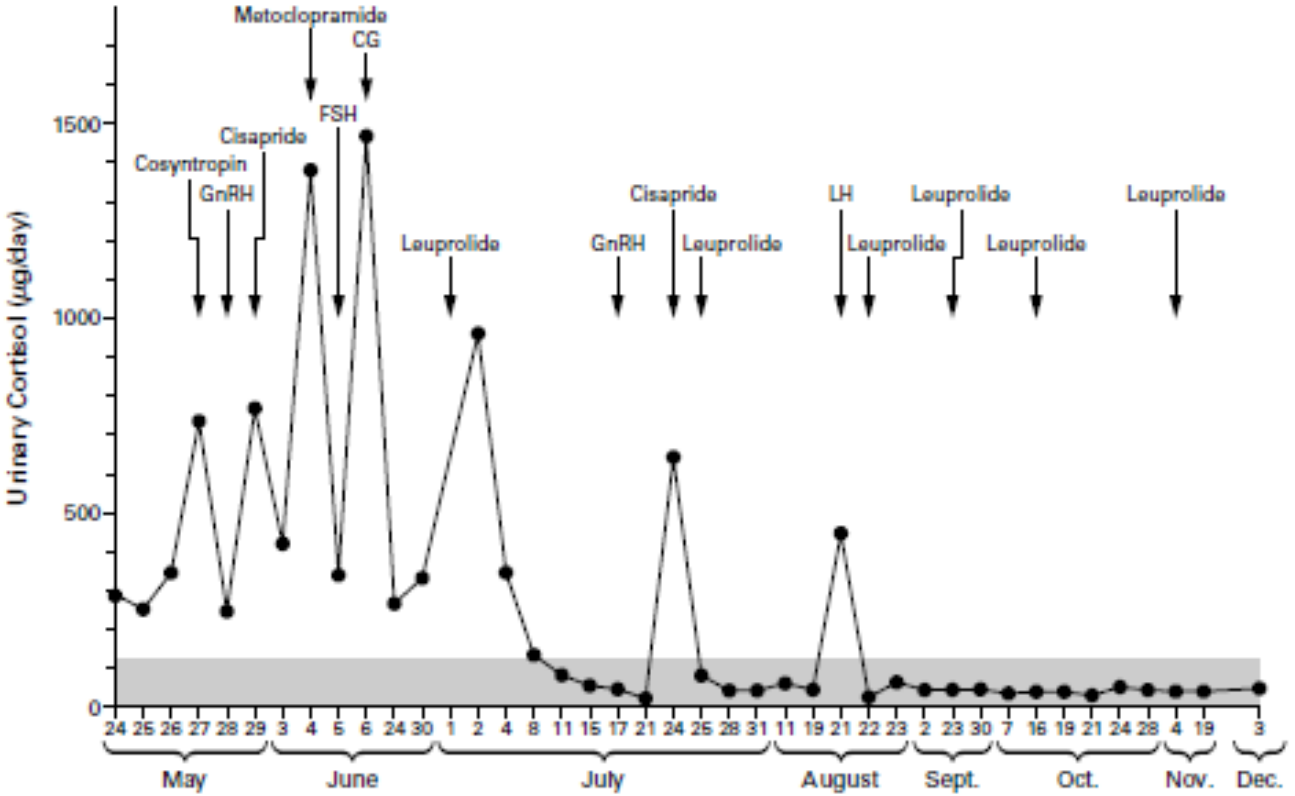
PROPRANOLOL THERAPY FOR ECTOPIC *b*-ADRENERGIC RECEPTORS IN ADRENAL CUSHING'S SYNDROME



Urinary Cortisol Excretion in a Patient with Cushing's Syndrome and Bilateral Macronodular Adrenal Hyperplasia during the Initial Studies and Treatment (Upper Panel) and after Left Adrenalectomy (Lower Panel).

Lacroix 1997

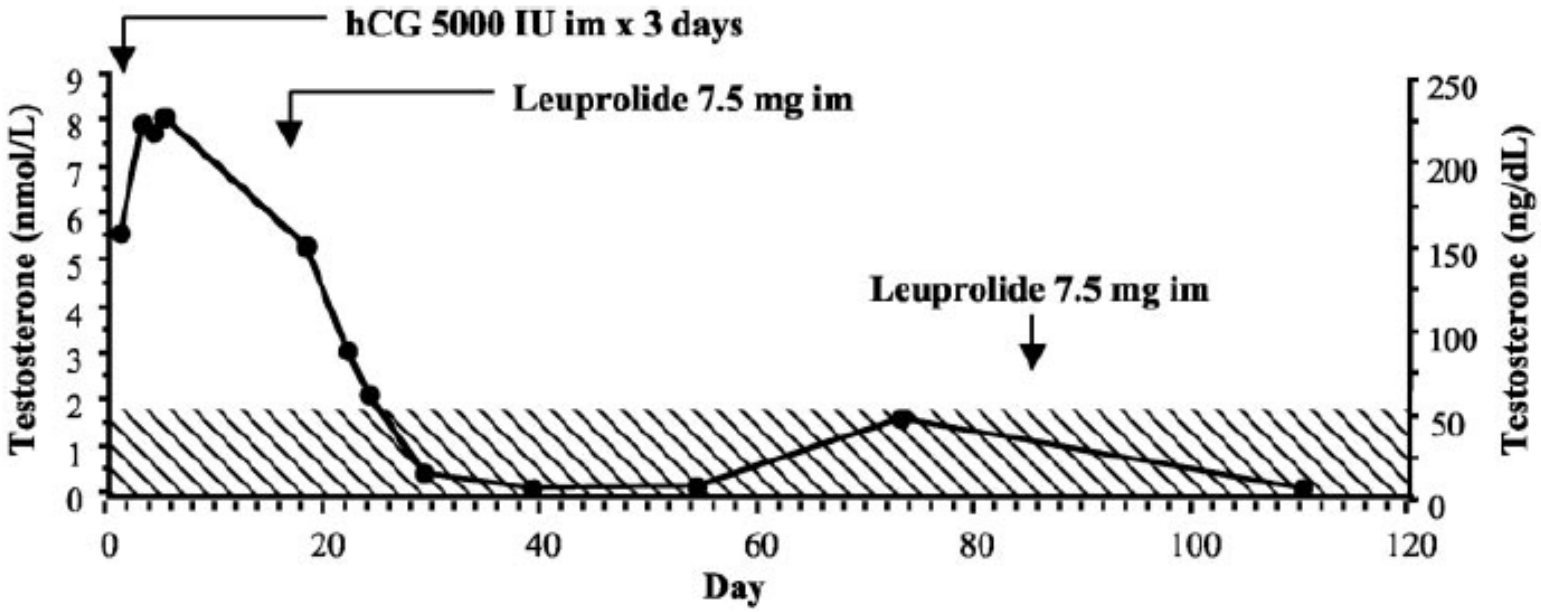
Leuprolide acetate therapy in Luteinizing hormone-dependent Cushing's syndrome



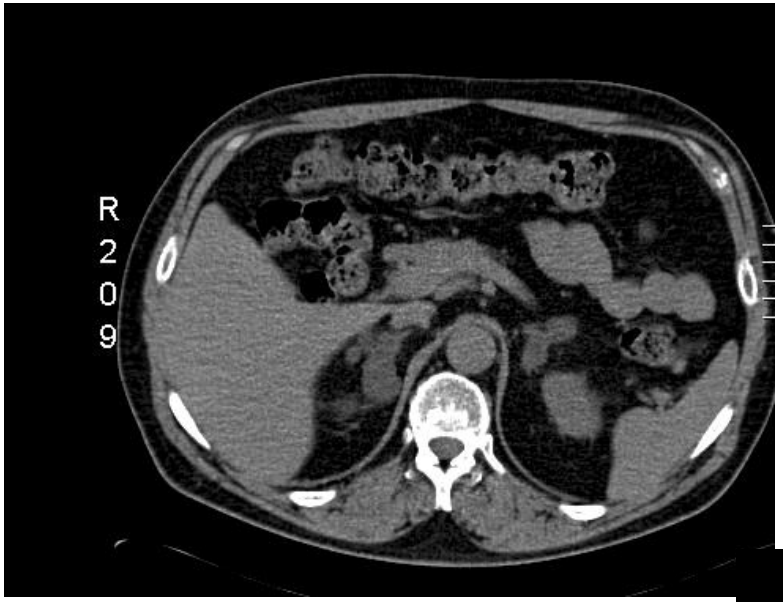
Urinary Cortisol Excretion in a Patient with Cushing's Syndrome and Bilateral Macronodular Adrenal Hyperplasia during Initial Studies and Treatment

Lacroix 1999

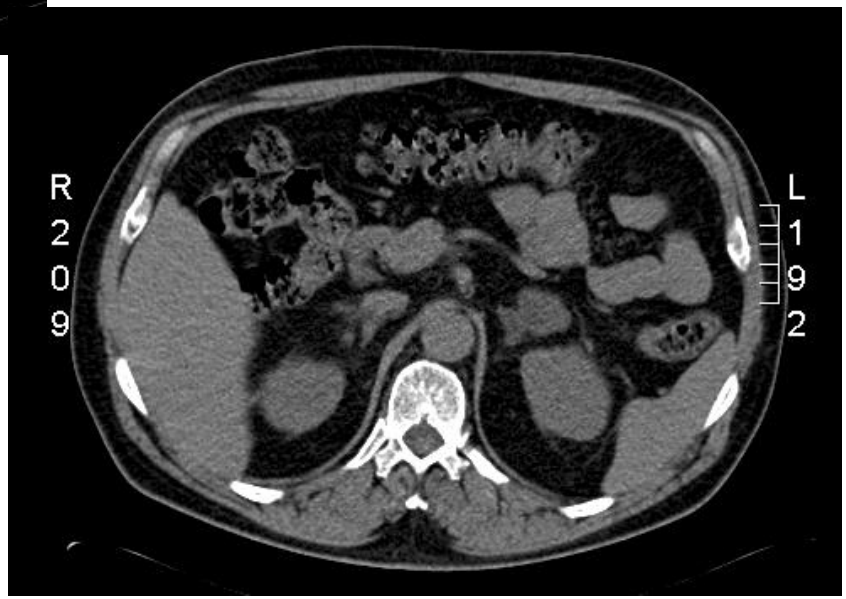
Virilization in Bilateral Macronodular Adrenal Hyperplasia Controlled by Luteinizing Hormone



Goodarzi 2003

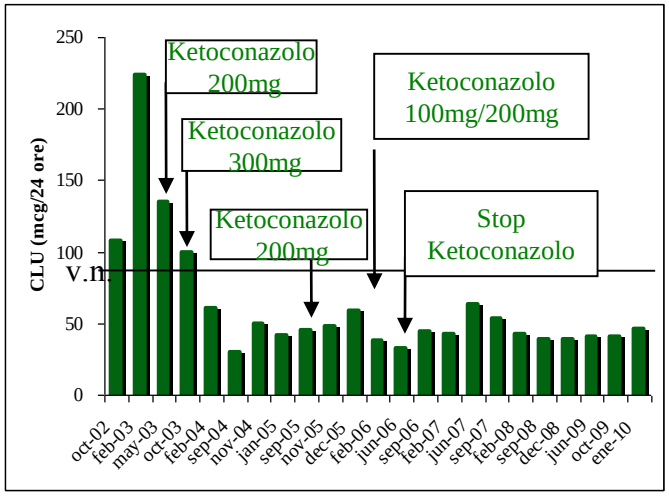


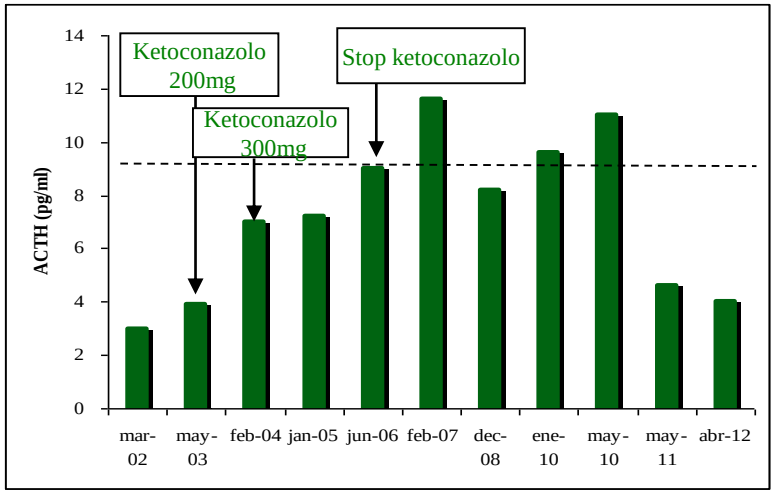
Soggetto obeso
iperteso
con ridotta tolleranza agli zuccheri
osteopenia
riscontro incidentale di masse surrenaliche bilaterali

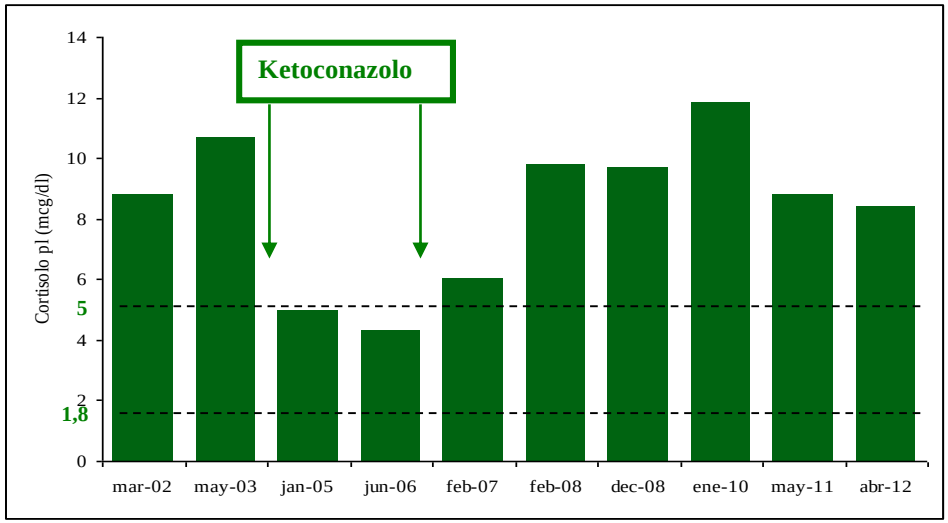


E R, 57aa

Trattamento con Ketoconazolo







E R, 57aa

Terapia chirurgica

European Journal of Endocrinology (2002) **146** 237–240 ISSN 0804-4643

CLINICAL STUDY

Is unilateral adrenalectomy an alternative treatment for ACTH-independent macronodular adrenal hyperplasia?: long-term follow-up of four cases

Cristina Lamas, José J Alfaro, Tomás Lucas, Beatriz Lecumberri, Balbino Barceló and Javier Estrada

Department of Endocrinology, Clínica Puerta de Hierro, University Hospital, Madrid, Spain

(Correspondence should be addressed to Javier Estrada, Department of Endocrinology, Clínica Puerta de Hierro, C/San Martín de Porres, 4. 28035 Madrid, Spain)

World J Surg (2008) 32:882–889
DOI 10.1007/s00268-007-9408-5

World Journal of Surgery

The Role of Unilateral Adrenalectomy in ACTH-Independent Macronodular Adrenal Hyperplasia (AIMAH)

Maurizio Iacobone · Nora Albiger · Carla Scaroni · Franco Mantero · Ambrogio Fassina · Giovanni Viel · Mauro Frego · Gennaro Favia

Iperplasia (displasia) micronodulare surrenalica ACTH indipendente

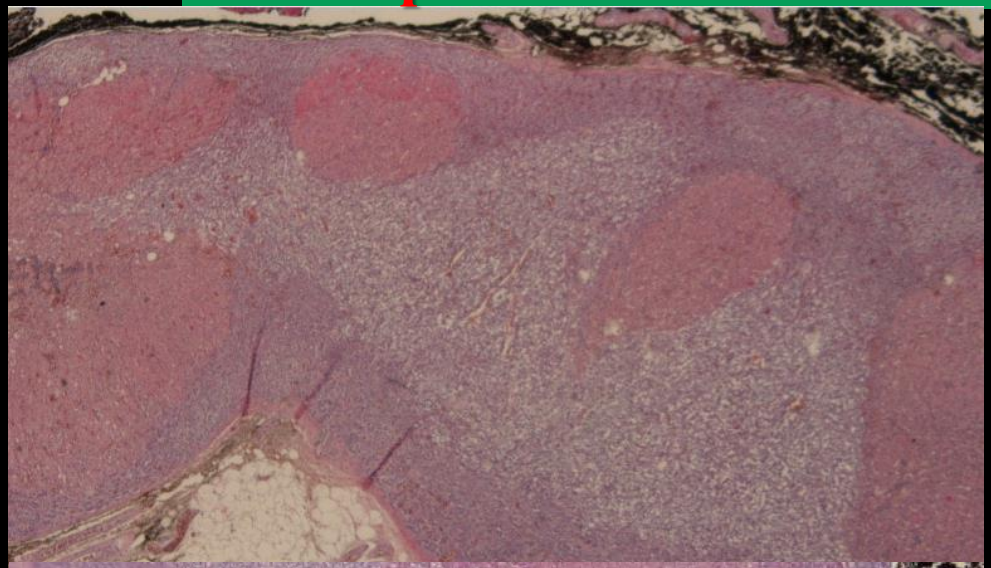
e la sua variante più frequente:

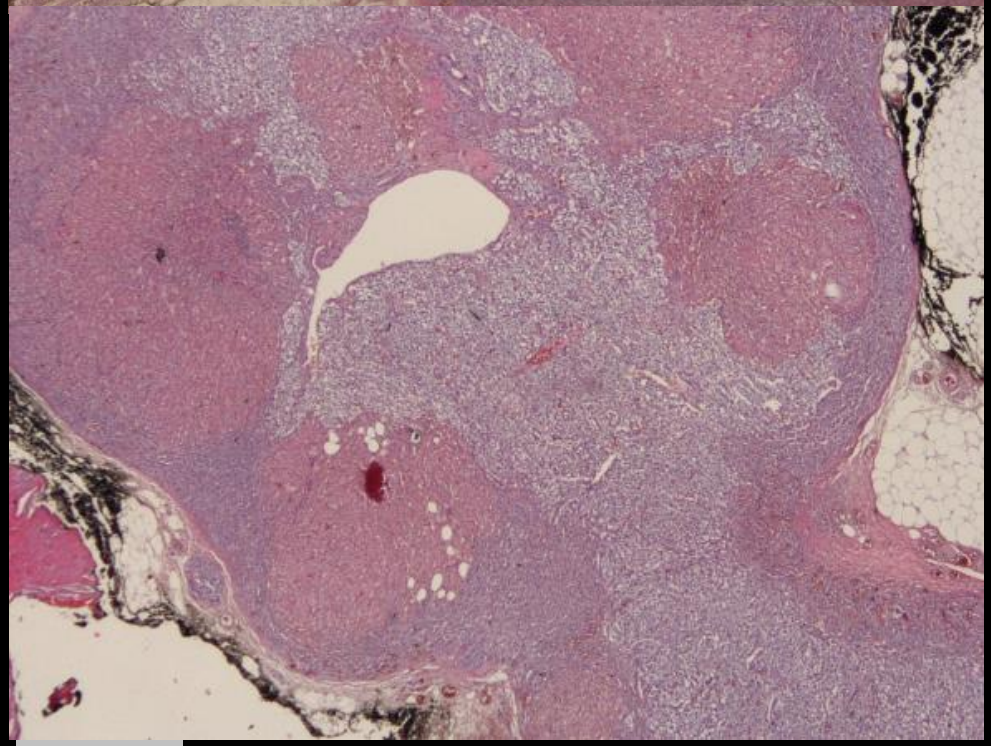
PPNAD
(sporadica o familiare)

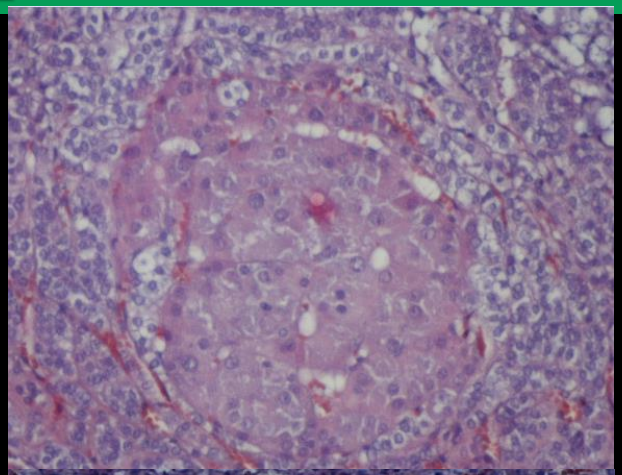
Iperplasia (displasia) micronodulare surrenalica ACTH indipendente – PRESENTAZIONE CLINICA

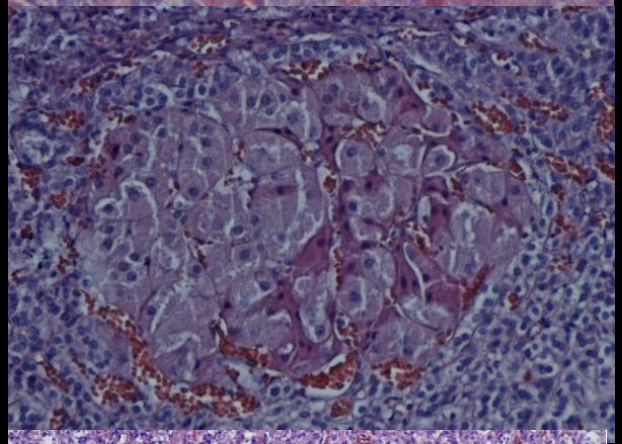
- **Malattia rara**
  Sporadica/ereditaria (PPNAD, Carney Complex)
- **Età giovanile (bambino, giovane adulto, raramente oltre 40 aa)**
- **Ipercortisolismo: lentamente progressivo, ciclico**
  raramente a remissione spontanea
- **Osteoporosi**
- **Non deficit staturale (forme cicliche)**
- **ACTH non completamente soppresso (forme lievi, cicliche)**
- **Risposta paradossa alla somministrazione di desametasone**

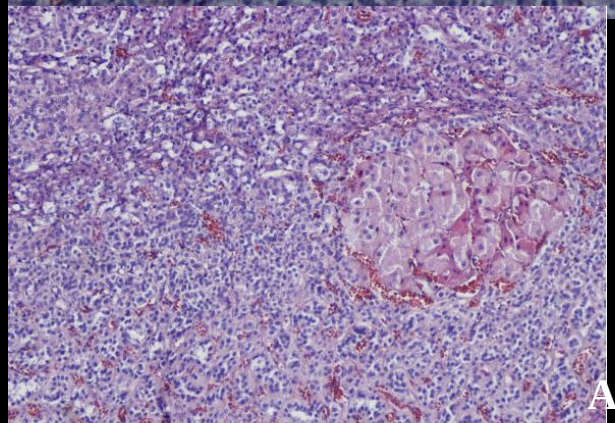
Iperplasia (displasia) micronodulare surrenalica ACTH indipendente – ISTOLOGIA











A.M,12 aa

MAJOR DIAGNOSTIC CRITERIA

Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)

Myxoma * (cutaneous and mucosal)

Cardiac myxoma *

Breast myxomatosis or fat suppressed magnetic resonance imaging findings suggestive of this diagnosis

PPNAD* or paroxical positive response of urinary glucocorticoid excretion to dexamethasone administration during Liddle's test

Acromegaly due to GH-producing adenoma*

LCCSCT or characteristic calcification on testicular ultrasound

Thyroid carcinoma* or multiple, hypoechoic nodules on thyroid ultrasound in a young patient

Psammomatous melanotic schwannomas*

Blue nevus, epithelioid blue nevus*

Breast ductal adenoma*

Osteochondromyxoma*

SUPPLEMENTAL CRITERIA

Affected first-degree relative

Inactivating mutation of the PRKAR1A gene

FINDINGS SUGGESTIVE OF OR POSSIBLY ASSOCIATED WITH CNC, BUT NOT DIAGNOSTIC FOR THE DISEASE

Intense freckling (without darkly pigmented spots or typical distribution)

Blue nevus, common type (if multiple)

Café-au-laits spots or other "birthmarks"

Elevated IGF-1 levels, abnormal OGTT, or paradoxical GH response to TRH testing in the absence of clinical acromegaly

Cardiomyopathy

Pilonidal sinus

History of Cushing's syndrome, acromegaly, or sudden death in extended family

Multiple skin tags or other skin lesions; lipomas

Colonic polyps (usually in association with acromegaly)

Hyperprolactinemia (usually mild and almost always combined with clinical or subclinical acromegaly)

Single, benign thyroid nodule in a young patient; multiple thyroid nodules in an older patient (detected on ultrasound)

Family history of carcinoma, in particular of the thyroid, colon, pancreas, and ovary; other multiple benign or malignant tumors

CNC: Carney complex; PPNAD: primary pigmented nodular adrenocortical disease; LCCSCT: large-cell calcifying Sertoli cell tumor; PRKAR1A: protein kinase A regulatory subunit 1alfa.

***After histological confirmation.**

From Almeida MQ, Stratakis CA, 2010.

Carney Complex e PPNAD/MAD

- **Displasia del surrene presente in tutti i pazienti**
- **S.Cushing conclamata in 25-45% dei casi**
- **S. Cushing atipica, periodica, subclinica nelle forme non conclamate**
- **PPNAD o MAD e S. Cushing come unica espressione di CNC**

eterogeneità clinica e patologica

A Large Family with Carney Complex Caused by the S147G PRKAR1A Mutation Shows a Unique Spectrum of Disease Including Adrenocortical Cancer

João Anselmo, Sandra Medeiros, Victor Carneiro, Elizabeth Greene, Isaac Levy, Maria Nesterova, Charalampos Lyssikatos, Anelia Horvath, J. Aidan Carney, and Constantine A. Stratakis

Carney Complex with Adrenal Cortical Carcinoma

Emilie Morin, Ozgur Mete, Jonathan D. Wasserman, Anthony Michael Joshua, Sylvia L. Asa, and Shereen Ezzat

Departments of Medicine (E.M., A.M.J., S.E.) and Pathology (O.M., S.L.A.), University Health Network, and Hospital for Sick Children (J.D.W.), Toronto, Ontario, Canada M5G 2N2

JCE&M 2012

GENETICA

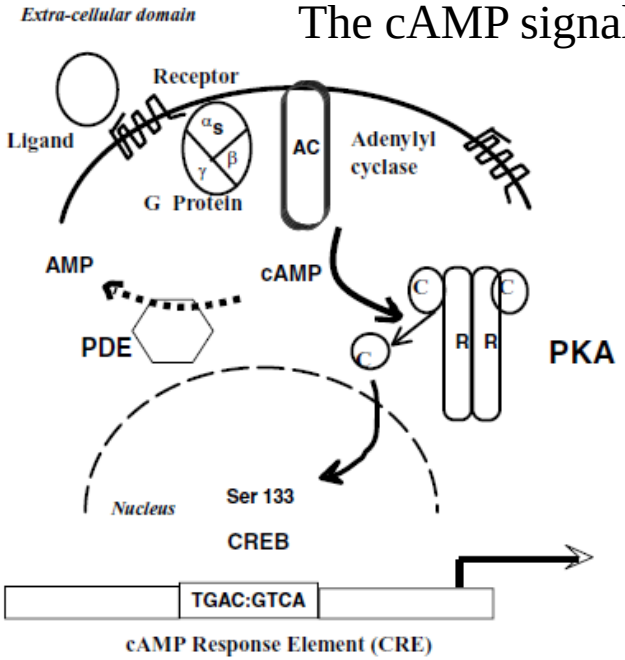
PRKAR1A

PDE11A

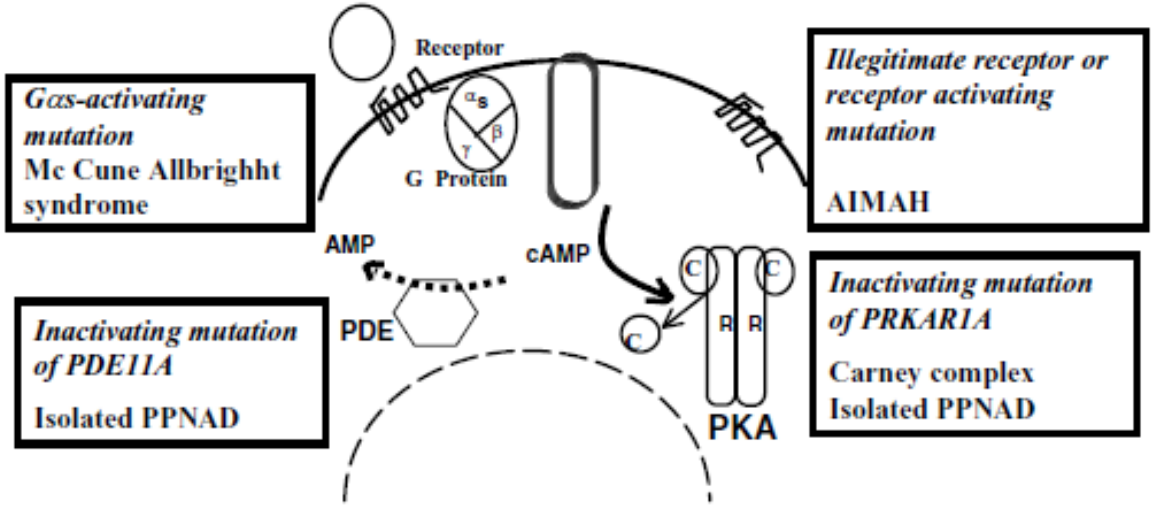
PDE8B

MYH8

The cAMP signalling pathway



Alterations in the cAMP signalling pathway



Cazabat 2006

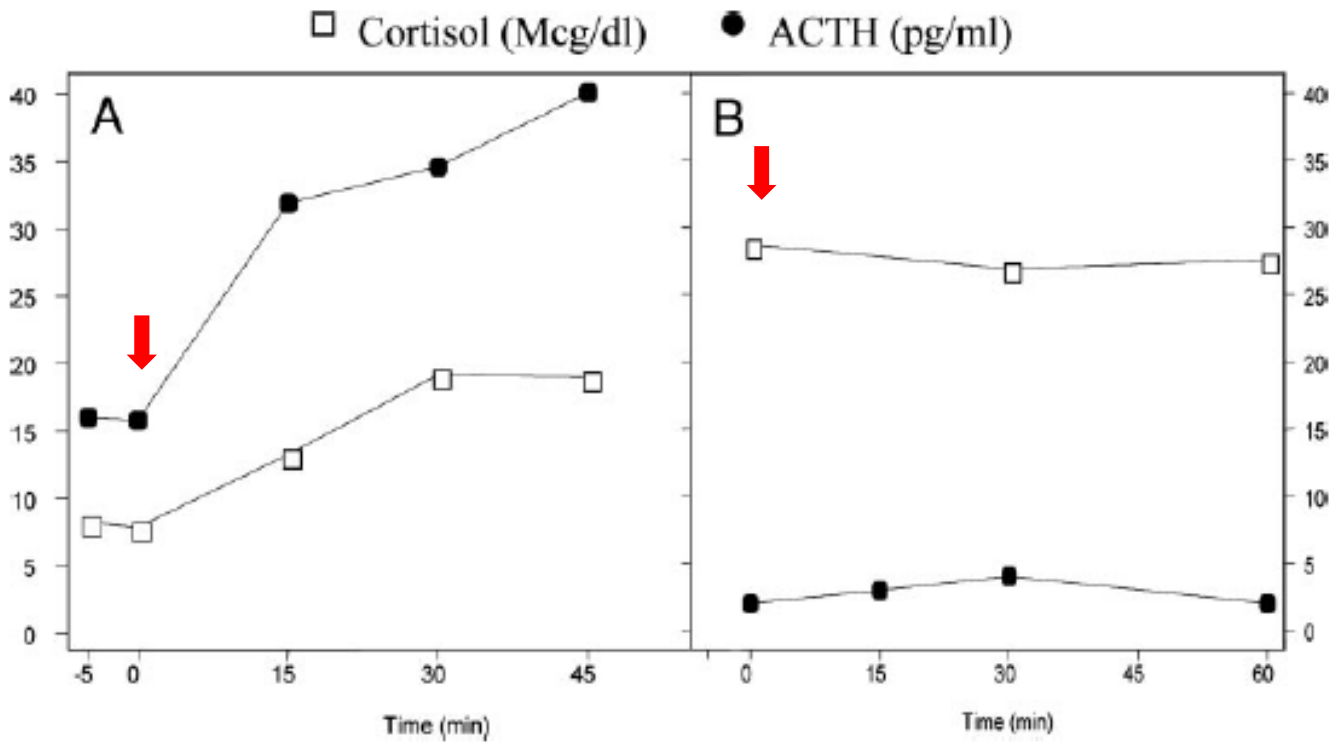
Iperplasia (displasia) micronodulare surrenalica ACTH indipendente – DIAGNOSI

- Dimostrazione di ipercortisolismo (forme familiari)
- Dimostrazione di forma ACTH indipendente
- Imaging
- Test di soppressione con Desametasone

Cyclical Cushing Syndrome Presenting in Infancy: An Early Form of Primary Pigmented Nodular Adrenocortical Disease, or a New Entity?

In remissione di malattia

In fase attiva di malattia

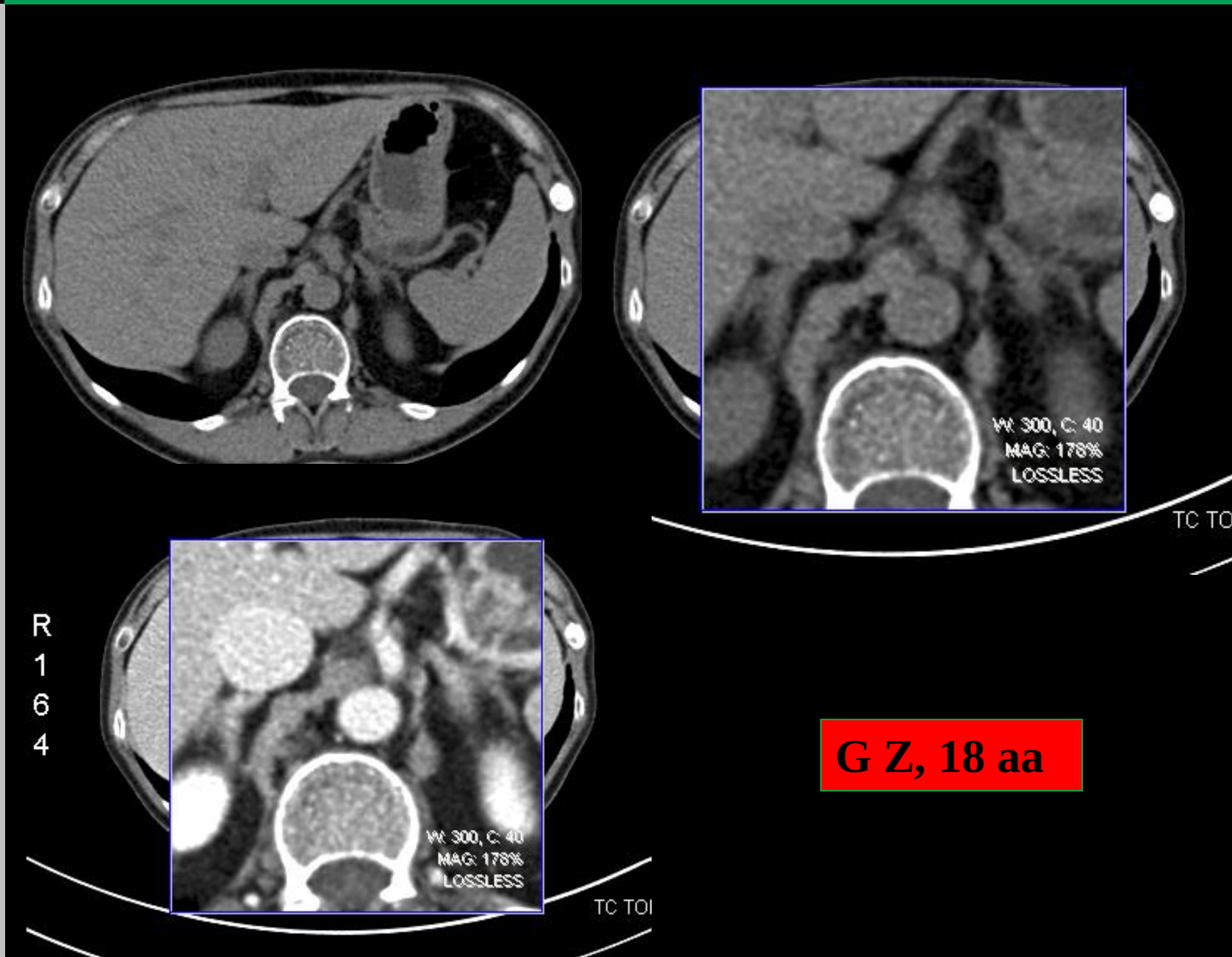


CRH 1 mcg/Kg

Gunther 2004

Iperplasia (displasia) micronodulare surrenalica ACTH indipendente – DIAGNOSI

- Dimostrazione di ipercortisolismo (forme familiari)
- Dimostrazione di forma ACTH indipendente
- Imaging
- Test di soppressione con Desametasone


W: 300, C: 40
MAG: 178%
LOSSLESS
TC TO
R
1
6
4
W: 300, C: 40
MAG: 178%
LOSSLESS
TC TOI

G Z, 18 aa

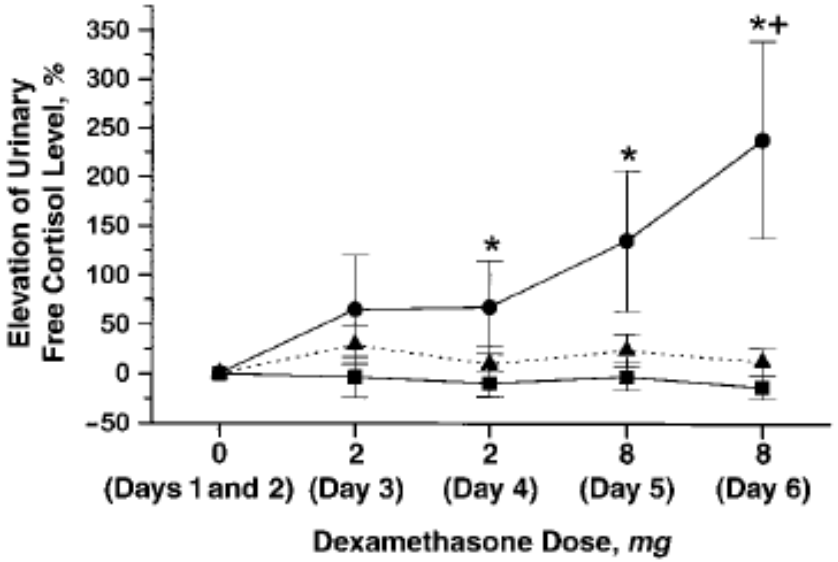
Rilievi radiologici indicativi di PPNAD

CT ad alta risoluzione con strato sottile 3 mm pre e post contrasto

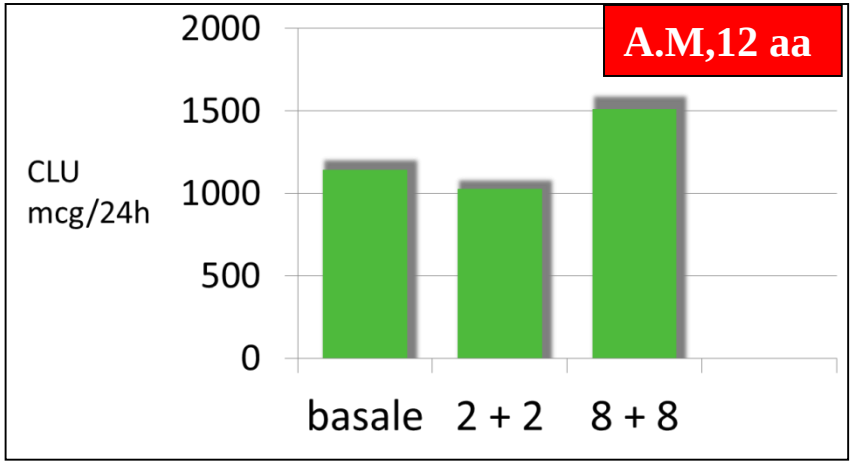
- Irregolarità del contorno delle ghiandole (anche se tenue)
- Presenza di uno o più spot ipodensi entro le ghiandole (pre- and post-contrasto)

Courcoutsakis 2013

Paradoxical Response to Dexamethasone in the Diagnosis of Primary Pigmented Nodular Adrenocortical Disease



- 21 PPNAD
- 9 AIMAH
- 15 ACA



Stratakis 1999

ORIGINAL ARTICLE

Endocrine Care

The Paradoxical Increase in Cortisol Secretion Induced by Dexamethasone in Primary Pigmented Nodular Adrenocortical Disease Involves a Glucocorticoid Receptor-Mediated Effect of Dexamethasone on Protein Kinase A Catalytic Subunits

Estelle Louiset, Constantine A. Stratakis, Véronique Perraudin, Kurt J. Griffin, Rossella Libé, Sylvie Cabrol, Bruno Fève, Jacques Young, Lionel Groussin, Jérôme Bertherat, and Hervé Lefebvre*

Louiset 2009

TERAPIA

- **Chirurgica**
- **Medica?**

TERAPIA CHIRURGICA

Surrenectomia bilaterale

- malattia surrenalica
- non rischio di recidiva
- ipofisi intrinsecamente normale
- non rischio di s. Nelson

Surrenectomia monolaterale

- non necessità di terapia sostitutiva

Operative management of Cushing Syndrome secondary to micronodular adrenal hyperplasia

1969-2006

34 pazienti MAD/PPNAD
(44% adulti,56% bambini)
FU medio 6,7 aa (range 1-27)

32 surrenectomie bilaterali,
41% laparoscopiche (cura 98%)

2 surrenectomie monolaterali
(persistenza di malattia, meno severa)

Powell 2008

World J Surg
DOI 10.1007/s00268-013-2059-9

World Journal of Surgery

The Role of Unilateral Adrenalectomy in Corticotropin-Independent Bilateral Adrenocortical Hyperplasias

Yunze Xu · Wenbin Rui · Yicheng Qi · Chongyu Zhang · Juping Zhao · Xiaojing Wang · Yuxuan Wu · Qi Zhu · Zhoujun Shen · Guang Ning · Yu Zhu

2000-2009

13 pazienti PPNAD
FU medio 3,9 aa (range 1-9)

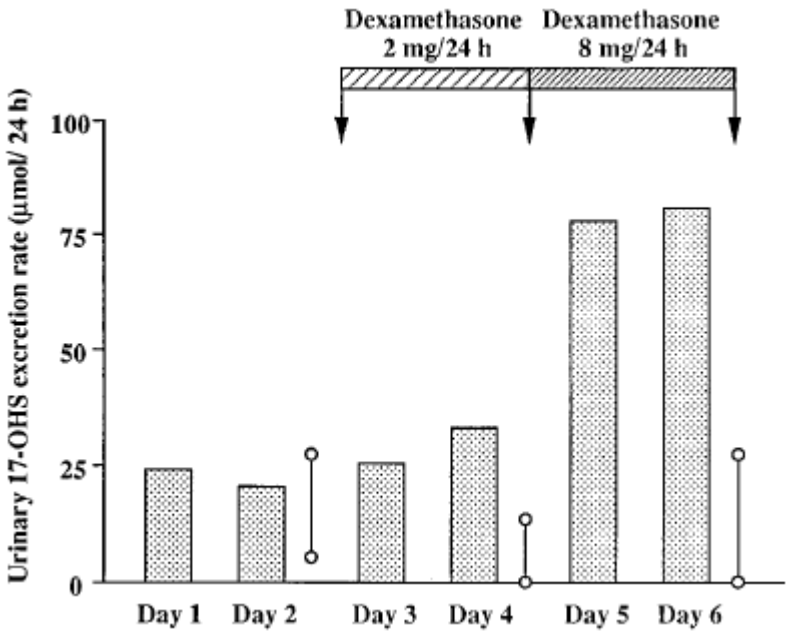
12 surrenectomie monolaterali (cura 92%, non valutabile)

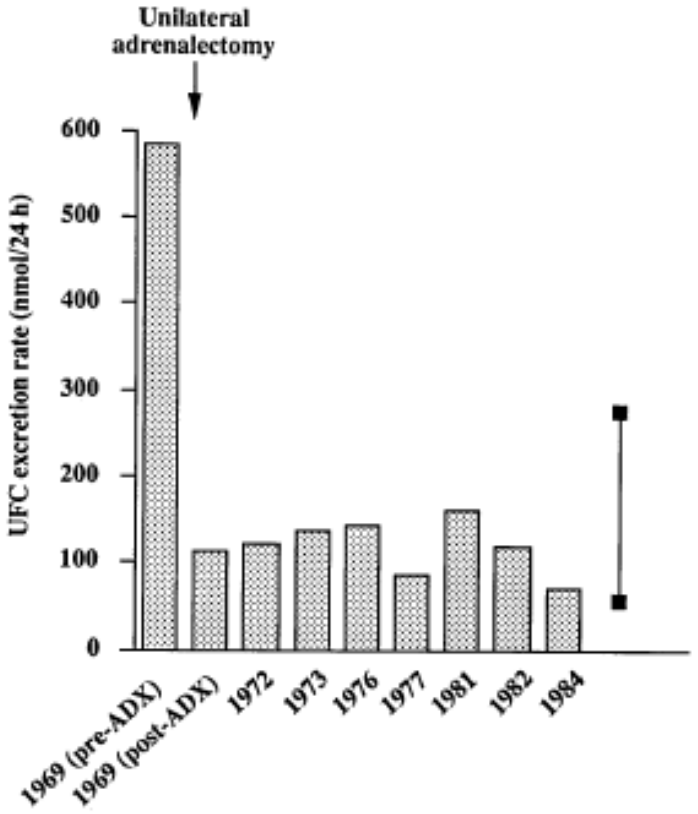
1 surrenectomia bilaterale

Surrenectomia monolaterale:

in caso di coinvolgimento asimmetrico dei surreni?

Primary Pigmented Nodular Adrenocortical Disease: Reevaluation of a Patient with Carney Complex 27 Years after Unilateral Adrenalectomy

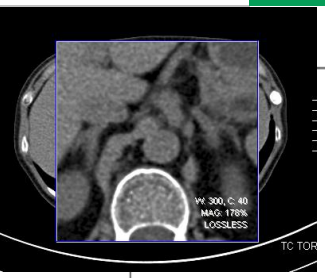


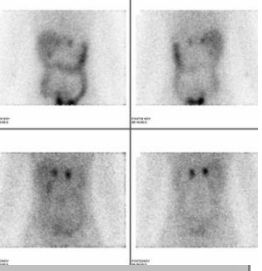


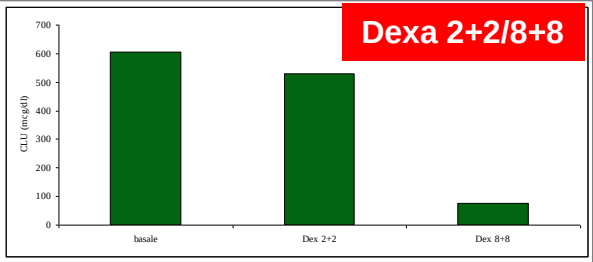
Test dexa pre surrenectomia

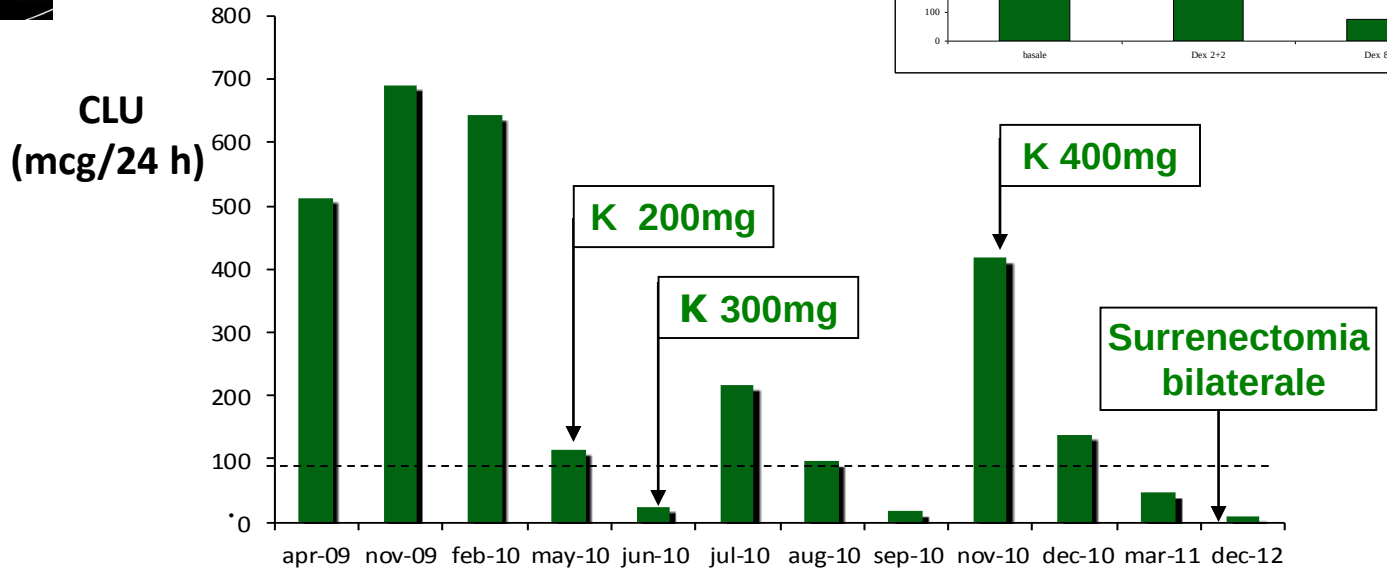
Sarlis 1997

TERAPIA MEDICA









K= ketoconazolo

G Z, 18 aa

Grazie per l'attenzione!

Azienda Ospedaliera
Niguarda Ca'
Granda