HIPERCORTISOLISMO POR HIPERPLASIA MACRONODULAR

Dra. Cristina Lamas

COMPLEJO HOSPITALARIO UNIVERSITARIO DE ALBACETE

UCLM
CAMPUS DE EXCELENCIA INTERNACIONAL
Facultad de Medicina de Albacete

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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)

Abstract

Objective: ACTH-independent macronodular adrenal hyperplasia is a rare cause of Cushing's syndrome. Bilateral adrenalectomy is considered the treatment of choice, but the patient is obliged to receive lifetime steroid replacement therapy and is susceptible to adrenal insufficiency crisis. New therapeutic alternatives are being proposed as new etiopathological features of the disease are known. Unilateral adrenalectomy of the largest gland can be a safe and effective alternative, but only short-term follow-up is reported in the literature. We present four consecutive patients with ACTH-independent macronodular hyperplasia and long-term remission of Cushing's syndrome after unilateral adrenalectomy.

Subjects: Four consecutive patients (two males and two females, mean age 50.3 years) with Cushing's syndrome due to ACTH-independent macronodular adrenal hyperplasia underwent unilateral adrenalectomy of the largest gland.

Results: The weight of the resected glands ranged from 26.8 to 210 g. Two patients suffered transient post-surgical adrenal insufficiency and had steroid replacement therapy for 60 and 14 months respectively. After a mean follow-up of 78.8 months (range 30–137 months) all the patients persist without any evidence of Cushing's syndrome. Urinary free cortisol and serum cortisol, after the adrenal insufficiency stage, have always stayed within their normal ranges, but cortisol circadian rhythm and suppressibility after dexamethasone have never normalized. No further enlargement of the contralateral gland has been documented 62 to 126 months after surgery in three of the four patients.

Conclusions: Unilateral adrenalectomy can be an effective and safe alternative treatment for ACTH-independent macronodular adrenal hyperplasia, and can achieve long-term remission of Cushing's syndrome.

CARACTERÍSTICAS CLÍNICAS

- 1% de síndrome de Cushing
- Ambas suprarrenales aumentadas de tamaño, con nódulos >1cm, a veces asimétrica y/o asincrónica
- Edad típica 40-60 años, predominio femenino (2,5:1)
- Esporádico / familiar
- Cushing leve o subclínico
- Esteroidogénesis poco eficiente

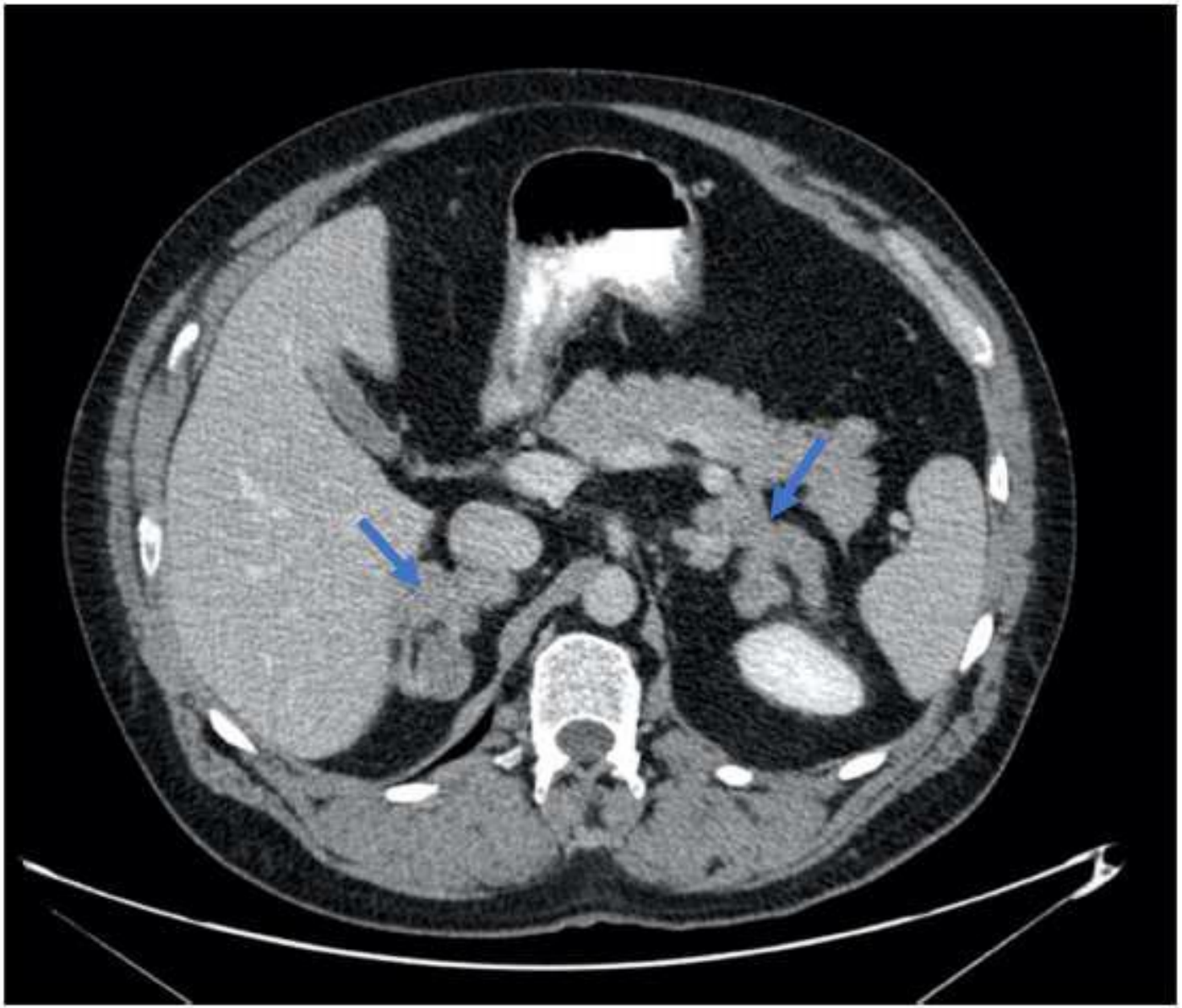


Figure 1.

PATOGENIA

- Expresión ocasional de receptores ectópicos
- Dependencia de ACTH de origen suprarrenal
- Mutaciones (gen *ARMC5* y otros*)*

Louiset et al. N Engl J Med 2013; 369:2115
Assié et al. N Engl J Med 2013; 369:2105

Receptores acoplados a proteínas G

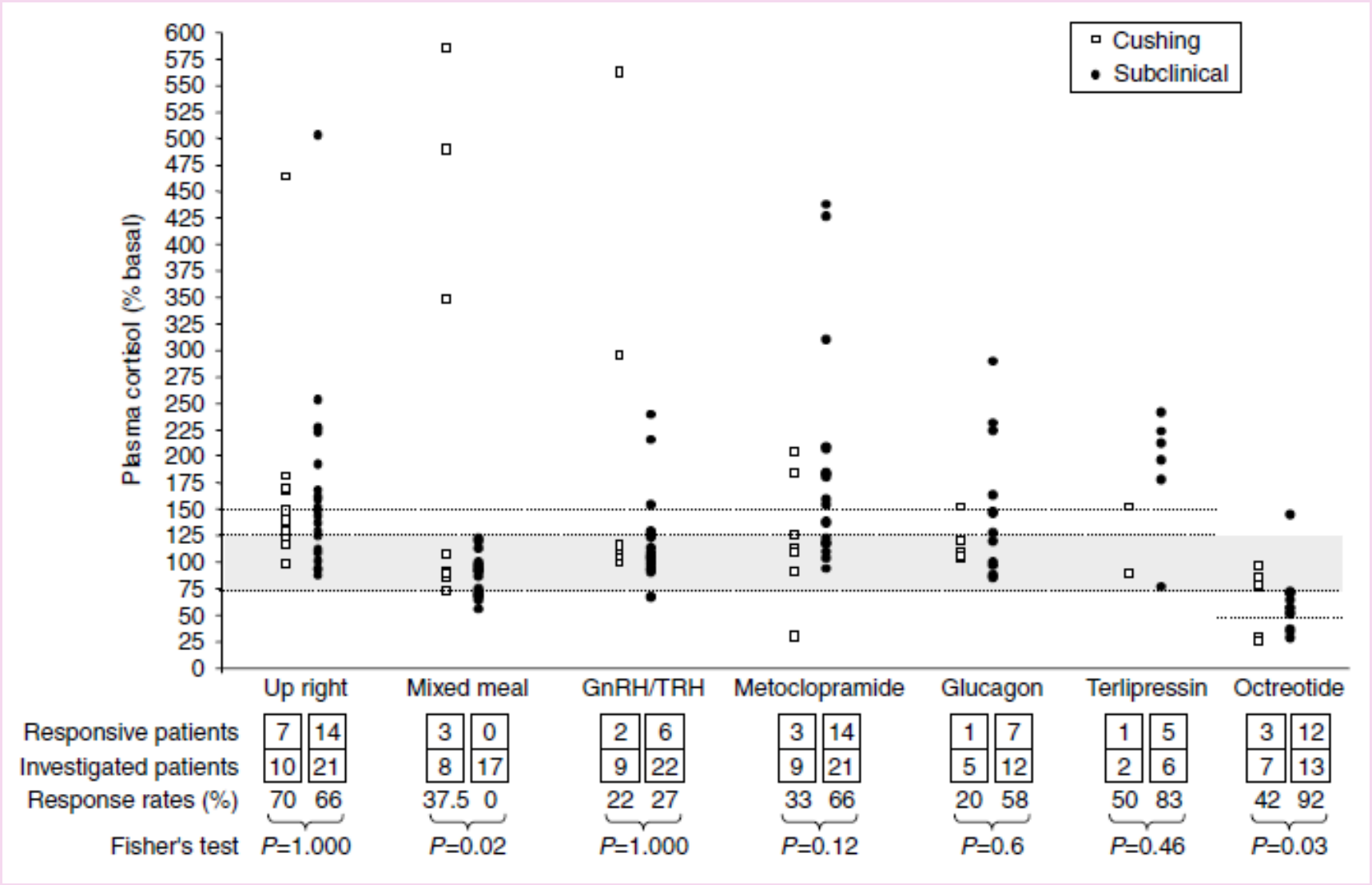
- Receptores ectópicos:
  - GIP
  - Catecolaminas
  - LH
- Receptores eutópicos, sobreexpresados:
  - Vasopresina (V1)
  - Serotonina
- 85% responden al menos a un estímulo, los más frecuentes:
  - Vasopresina
  - Serotonina
  - LH/hCG
  - GIP

Lacroix A, N'Diaye N, Bordeaux I

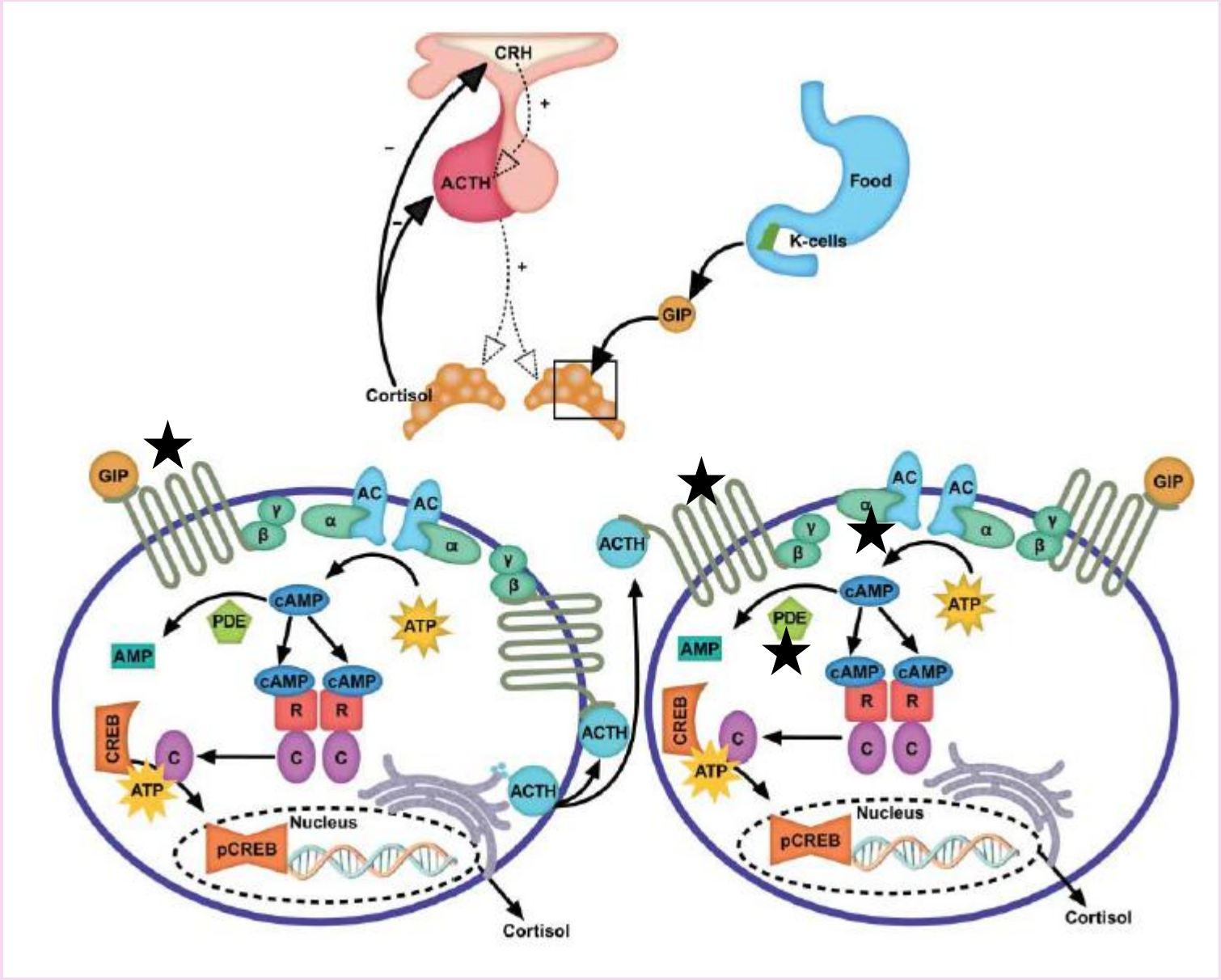
Protocolo de estudio de receptores anómalos

- Día 1:
  - bipedestación (angiotensina-II, vasopresina, catecolaminas, endotelina, péptido natriurético)
  - Comida mixta (GIP)
  - ACTH 250 mcg
- Día 2:
  - GnRH
  - TRH
- Día 3:
  - glucagón
  - metoclopramida (agonista serotoninérgico 5HT4)
  - (octreotide)

Lacroix A et al. Endoc Rev 2001; 22(1): 75–110



Libé et al. Eur J Endocrinol 2010; 163:129 (n=32)



El Ghorayeb et al. Eur J Endocrinol 2015; 173, M45–M60

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Louiset et al. N Engl J Med 2013; 369:2115
Assié et al. N Engl J Med 2013; 369:2105

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intraadrenal Corticotropin in Bilateral Macronodular Adrenal Hyperplasia

Estelle Louiset, Ph.D., Céline Duparc, Ph.D., Jacques Young, M.D., Ph.D., Sylvie Renouf, Ph.D., Milène Tetsi Nomigni, M.Sc., Isabelle Boutelet, Ph.D., Rossella Libé, M.D., Zakariae Bram, M.Sc., Lionel Groussin, M.D., Ph.D., Philippe Caron, M.D., Antoine Tabarin, M.D., Ph.D., Fabienne Grunenberger, M.D., Sophie Christin-Maitre, M.D., Ph.D., Xavier Bertagna, M.D., Ph.D., Jean-Marc Kuhn, M.D., Youssef Anouar, Ph.D., Jérôme Bertherat, M.D., Ph.D., and Hervé Lefebvre, M.D., Ph.D.

ABSTRACT

DEPENDENCIA DE ACTH DE ORIGEN SUPRARRENAL

- Estudian la producción suprarrenal de ACTH en 30 muestras de tejido de BMAH:
  - mRNA de POMC (26/26)
  - IHQ para ACTH (25/25, 5 aisladas, 21 en *clusters*) (correlación con cortisol sérico)
  - Producción de ACTH y cortisol en cultivos celulares
  - Aumento de ACTH en respuesta a receptores aberrantes (GIP / serotonina / hCG) y no a CRH / DXM / mifepristone
  - Cortistatina redujo cortisol 40%
  - In vivo (cateterismo, 2 pacientes):
  - mayor concentración de ACTH en venas suprarrenales que en vena periférica

Louiset et al. N Engl J Med 2013; 369:2115

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

ARMC5 Mutations in Macronodular Adrenal Hyperplasia with Cushing's Syndrome

Guillaume Assié, M.D., Ph.D., Rossella Libé, M.D., Stéphanie Espiard, M.D., Marthe Rizk-Rabin, Ph.D., Anne Guimier, M.D., Windy Luscap, M.Sc., Olivia Barreau, M.D., Lucile Lefèvre, M.Sc., Mathilde Sibony, M.D., Laurence Guignat, M.D., Stéphanie Rodriguez, M.Sc., Karine Perlemoine, B.S., Fernande René-Corail, B.S., Franck Letourneur, Ph.D., Bilal Trabulsi, M.D., Alix Poussier, M.D., Nathalie Chabbert-Buffet, M.D., Ph.D., Françoise Borson-Chazot, M.D., Ph.D., Lionel Groussin, M.D., Ph.D., Xavier Bertagna, M.D., Constantine A. Stratakis, M.D., Ph.D., Bruno Ragazzon, Ph.D., and Jérôme Bertherat, M.D., Ph.D.

ABSTRACT

ARMC5

- Secuenciación del genoma completo en 33 pacientes con BMAH (sangre periférica y tumor)
- 18/33 (55%) tenían mutación germinal en ARMC5 (16p11.2)
- Mutación germinal + mutación somática (diferentes mutaciones en diferentes nódulos de un mismo paciente)
- La inactivación de ARMC5 se asoció a menor esteroidogénesis *in vitro*

Assié et al. N Engl J Med 2013; 369:2105

JCEM ONLINE

Advances in Genetics—Endocrine Research

Macronodular Adrenal Hyperplasia due to Mutations in an Armadillo Repeat Containing 5 (*ARMC5*) Gene: A Clinical and Genetic Investigation

Fabio R. Faucz,* Mihail Zilbermint,* Maya B. Lodish, Eva Szarek, Giampaolo Trivellin, Ninet Sinaii, Annabel Berthon, Rossella Libé, Guillaume Assié, Stéphanie Espiard, Ludivine Drougat, Bruno Ragazzon, Jerome Bertherat,* and Constantine A. Stratakis*

Section on Endocrinology and Genetics (F.R.F., M.Z., M.B.L., E.S., G.T., A.B., C.A.S.), Program on Developmental Endocrinology and Genetics, Program on Reproductive and Adult Endocrinology (M.Z.), Biostatistics and Clinical Epidemiology Service (N.S.), Clinical Center, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892; Group for Advanced Molecular Investigation (F.R.F.), Graduate Program in Health Science, Center for Biological and Sciences, Pontificia Universidade Catolica do Paraná, Curitiba Brazil 80215-901; Department of Endocrinology, Metabolism, and Cancer (R.L., G.A., S.E., L.D., B.R., J.B.), INSERM Unité 1016, Centre National de la Recherche Scientifique Unité Mixte de Recherche 8104, Institut Cochin, 75014 Paris, France

- Serie de 34 pacientes con BMAH
  - 15 portadores de mutaciones en ARMC (2 familiares, 13 esporádicos), sólo 7 aparentemente patogénicas (20,6%)
  - Menor ACTH y mayor cortisol nocturno en pacientes con mutación

Faucz et al. JCEM201; 99(6):E1113-9

Endocrine
DOI 10.1007/s12020-016-0956-z

ORIGINAL ARTICLE

A multicenter experience on the prevalence of ARMC5 mutations in patients with primary bilateral macronodular adrenal hyperplasia: from genetic characterization to clinical phenotype

N. M. Albiger[1] · D. Regazzo[1] · B. Rubin[1] · A. M. Ferrara[2] · S. Rizzati[2] · E. Taschin[2] · F. Ceccato[1] · G. Arnaldi[3] · F. Pecori Giraldi[4,5] · A. Stigliano[6] · L. Cerquetti[6] · F. Grimaldi[7] · E. De Menis[8] · M. Boscaro[1] · M. Iacobone[9] · G. Occhi[10] · C. Scaroni[1]

Received: 11 February 2016 / Accepted: 7 April 2016

- 71 pacientes con BMAH:
  - 53 con hipercortisolismo: 12 con mutación ARMC5 (2 familiar, 10 esporádicos) (10/51, 19,6%). Tenía suprarrenales más grandes, más HTA, más diabetes.
  - 18 no secretores (ninguna mutación ARMC5)
  - Ambos sexos en mutados. Predominio femenino en no mutados.

Endocrine
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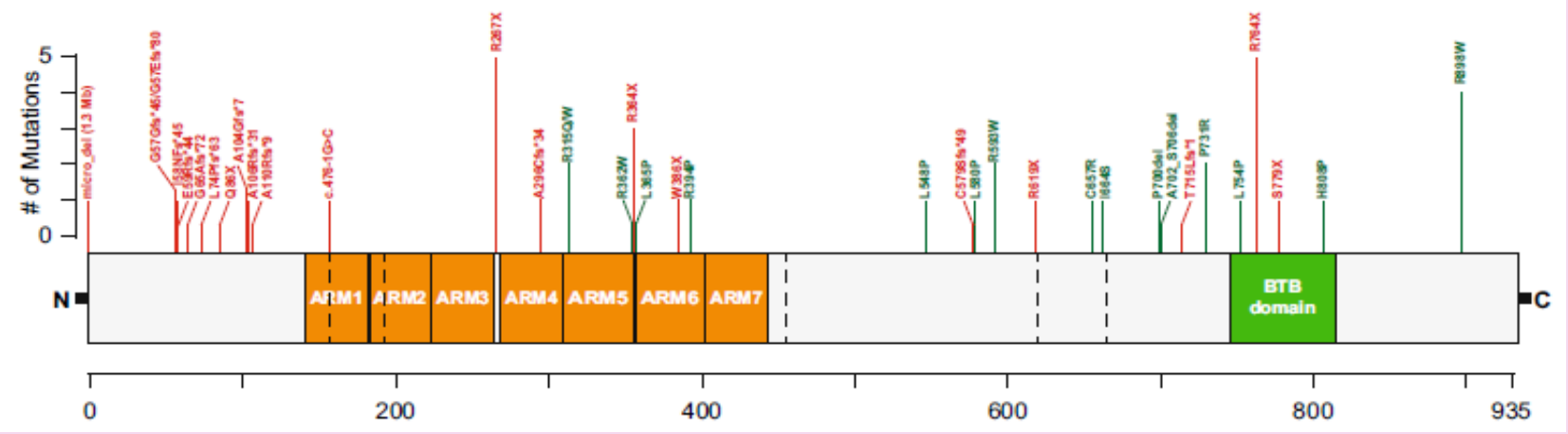


JCEM ONLINE

Advances in Genetics

ARMC5 Mutations in a Large Cohort of Primary Macronodular Adrenal Hyperplasia: Clinical and Functional Consequences

Stéphanie Espiard,* Ludivine Drougat,* Rossella Libé,* Guillaume Assié,* Karine Perlemoine, Laurence Guignat, Gaelle Barrande, Françoise Brucker-Davis, Françoise Doullay, Stephanie Lopez, Emmanuel Sonnet, Florence Torremocha, Denis Pinsard, Nathalie Chabbert-Buffet, Marie-Laure Raffin-Sanson, Lionel Groussin, Françoise Borson-Chazot, Joël Coste, Xavier Bertagna, Constantine A. Stratakis, Felix Beuschlein, Bruno Ragazzon, and Jérôme Bertherat†

Espiard et al. J Clin Endocrinol Metab 2015; 100: E926–E935

J Clin Endocrinol Metab 100: E926–E935, 2015

Table 1. Clinical and Hormonal Characteristics of PBMAH Patients

Characteristics	Total Cohort[a,b]	Mutated[a,b]	Wild-Type[a,b]	*P* Value[c]
Number of patients	98	24	68	
Age, y	53 [30–75]	49 [30–73]	55 [32–75]	.046
Sex (F/M), %	64.3/35.7	50/50	69.1/30.9	.137
CS, %				.007
Clinical	43	71	35	
Subclinical	47	29	53	
Absent	10	0	11.8	
Hypertension, %[d]	69.3	94.7	63.5	.009
Diabetes, %[d]	33.7	52.9	30.2	.093
Hypokalemia, %[d]	12.9	17.6	11.3	.441
ACTH, %[e]				.003
<10 pg/mL	60	92	53	
10 to 15 pg/mL	30	8	34	
>15 pg/mL	9	0	12	
UFC (% of increase above upper limit of normal)[e]	204 [11–2433]	355 [11–1626]	167 [16–2433]	.006
Plasma cortisol after 1 mg dexamethasone overnight test, μg/dL[e]	9.9 [0.3–36.7]	18.6 [3.6–36.7]	6.3 [0.3–2.7]	<.001
Plasma cortisol at midnight, μg/dL[e]	12.1 [1.4–71.7]	20 [4.6–71.7]	9.4 [1.4–42.8]	.019
Morning plasma cortisol, μg/dL[e]	14.1 [4.7–57.1]	16.9 [5.5–34]	13.8 [4.7–57.1]	.245
Plasma cortisol after ACTH 1–24 250 μg, μg/dL[e]	39.2 [11.1–123]	48.9 [19.8–81.3]	37 [11.1–123]	0.058
Basal 17OHP, ng/dL[e]	99 [0–726]	132 [0–594]	99 [0–726]	.28
17OHP after ACTH 1–24 250 μg, ng/dL[e]	990 [132–7128]	1089 [264–5578]	990 [132–7128]	.79
Aldosterone/direct renin ratio, pmol/L/μIU/mL[e]	22 [0–331]	33 [0–331]	19 [0–133]	.45
Food response, %[d]	17.6	0	28.1	<.001
Upright response, %[d]	52.9	68.8	46.9	.221

- Más tejido suprarrenal (diámetro en TAC, número de nódulos, peso en cirugía)

Yu et al. PLoS ONE 2018; 13(1): e0191602

RESEARCH ARTICLE

ARMC5 mutations in familial and sporadic primary bilateral macronodular adrenal hyperplasia

Liping Yu[1], Junqing Zhang[1]*, Xiaohui Guo[1], Xiaoyu Chen[1], Zhisong He[2], Qun He[2]

1 Deparment of Endocrinology and Metabolism, Peking University First Hospital, Xicheng District, Beijing, China, 2 Department of Urology, Peking University First Hospital, Xicheng District, Beijing, China

- 3 familias con BMAH hereditaria:
  - 12 portadores de mutaciones patogénicas en ARMC
    (2 asintomáticos con 23 y 29 años)
- 23 pacientes esporádicos con BMAH:
  - 5 con mutación ARMC5 (22%)
  - Sin diferencias en edad, sexo, IMC, CLU, cortisol tras DXM, HTA, diabetes.

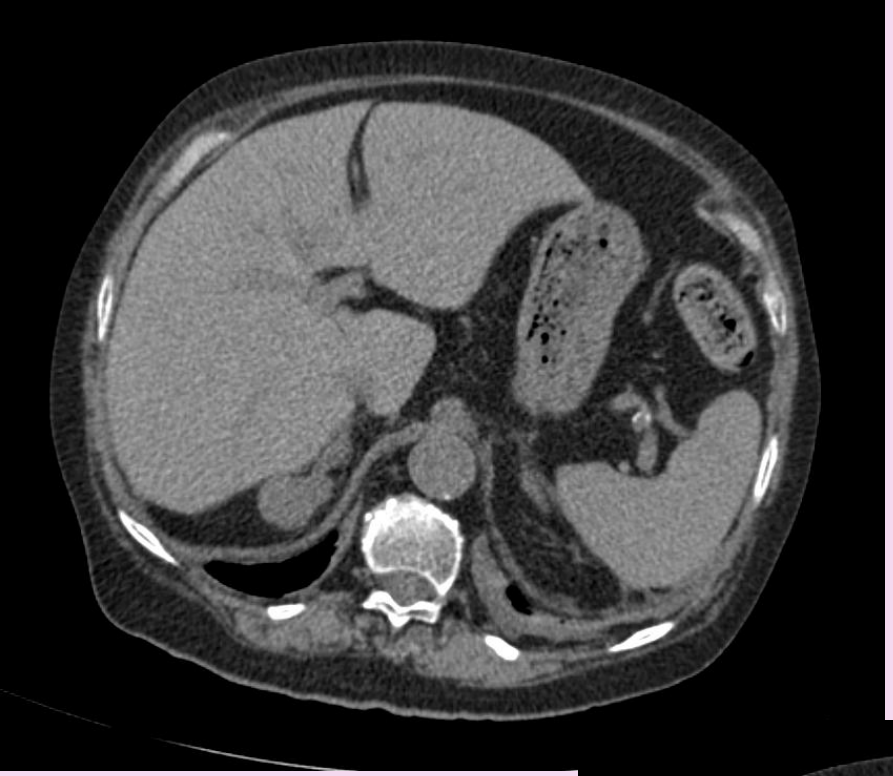
OTROS GENES POSIBLEMENTE IMPLICADOS

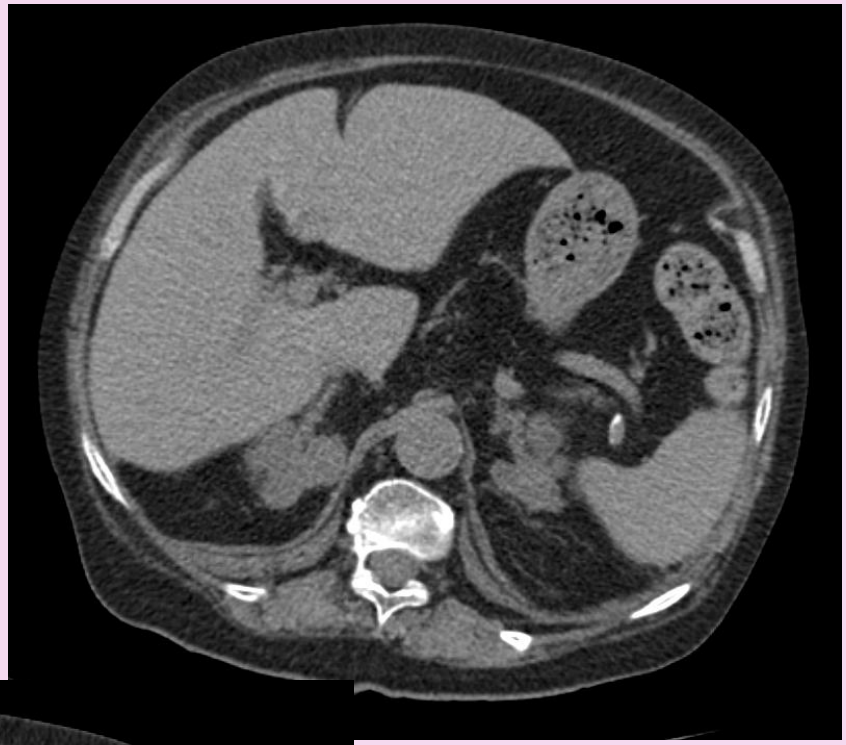
Gene	Locus	Function of the WT protein	Associated manifestations
ARMC5	16p11	No known function, potential role in regulation of apoptosis and steroidogenesis	Meningioma?
Menin	11q13	Regulator of gene transcription, cell proliferation, apoptosis, and genome stability	Multiple endocrine neoplasia type 1 (MEN1): hyperparathyroidism, pituitary adenomas, pancreatic neuroendocrine tumors
FH	1q42	Krebs cycle, amino acid metabolism	Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)
PDE11A	2q31-35	Hydrolysis of cAMP and cGMP	Isolated
GNAS1	20q13	Stimulation of adenyl cyclase, activation of the cAMP/PKA pathway	McCune Albright syndrome: fibrous bone dysplasia, café-au-lait spots, precocious puberty, acromegaly, toxic multinodular goiter
APC	5q12-22	Prevent β-catenin accumulation, inhibition of the Wnt/β-catenin pathway	Familial adenomatous polyposis: colon adenomas and carcinomas, pigmented retinal lesions, desmoids tumors, other malignant tumors as adrenocortical carcinomas
MC2R	18p11	ACTH receptor, activation of the cAMP/PKA pathway	Isolated
PRKACA	19p13.1	Catalytic subunit of PKA, activation of the cAMP/PKA pathway	

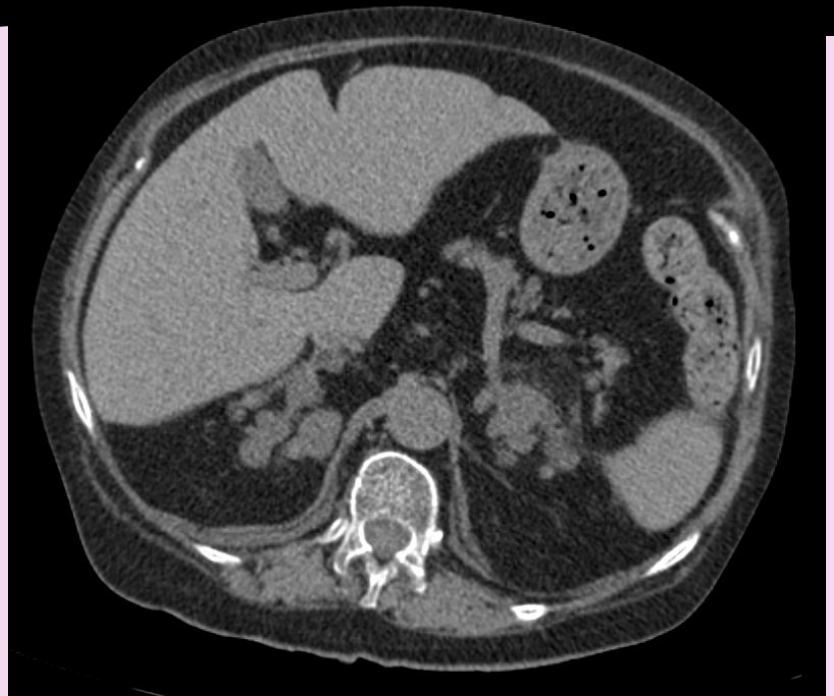
Drougat et al. Eur J Endocrinol 2015; 173:M121-31

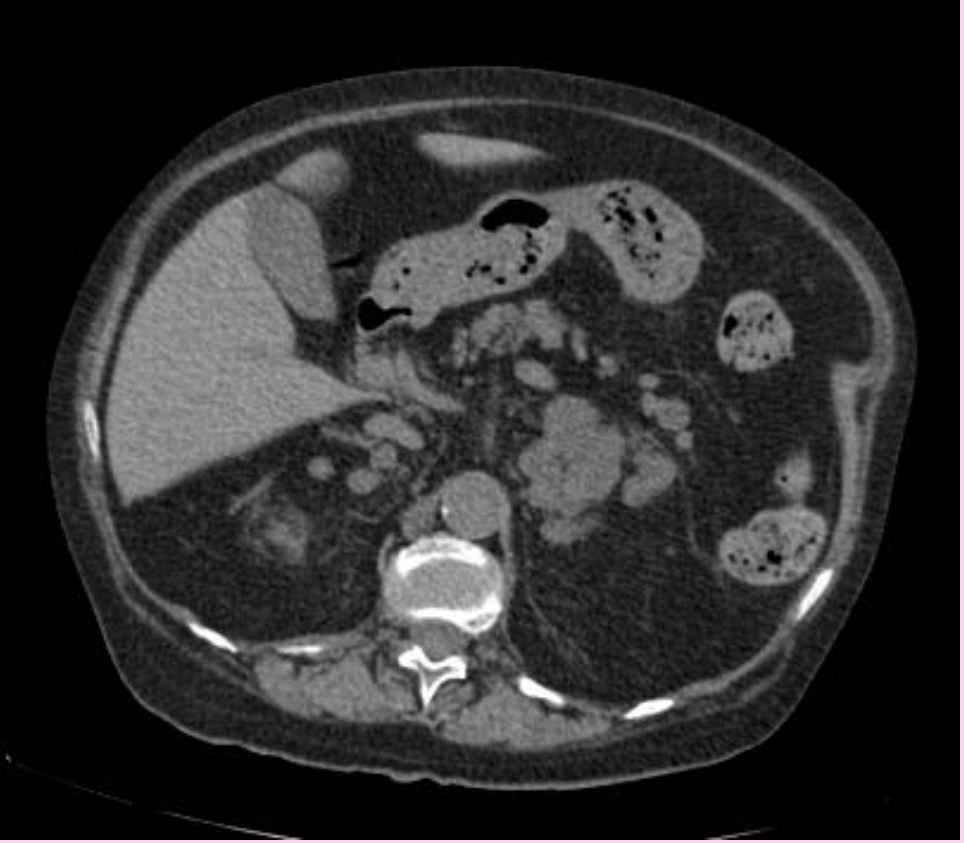
EVALUACIÓN DIAGNÓSTICA

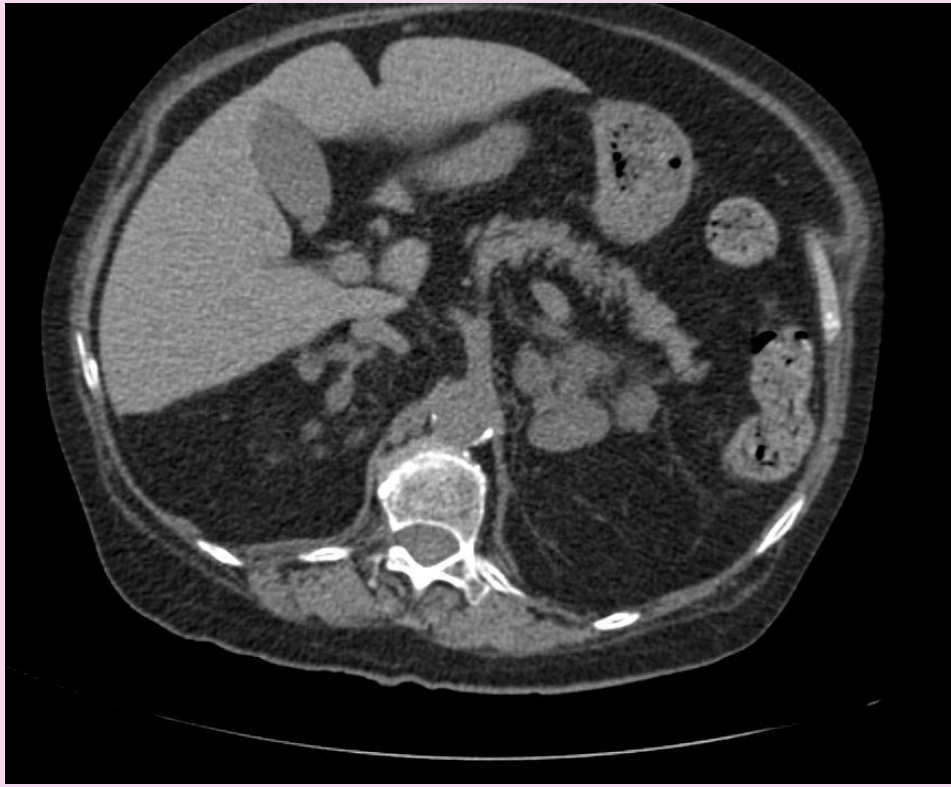
- Como otros incidentalomas suprarrenales bilaterales
- 1 mg DXM
  - Si patológico, CLU, ACTH, ¿cortisol nocturno?
- Metanefrinas
- Aldosterona / ARP
- Cortisol basal
- 17-OH-progesterona
- Evaluar repercusiones del hipercortisolismo: diabetes, HTA, osteoporosis…
- ¿Protocolo de estudio de receptores aberrantes?

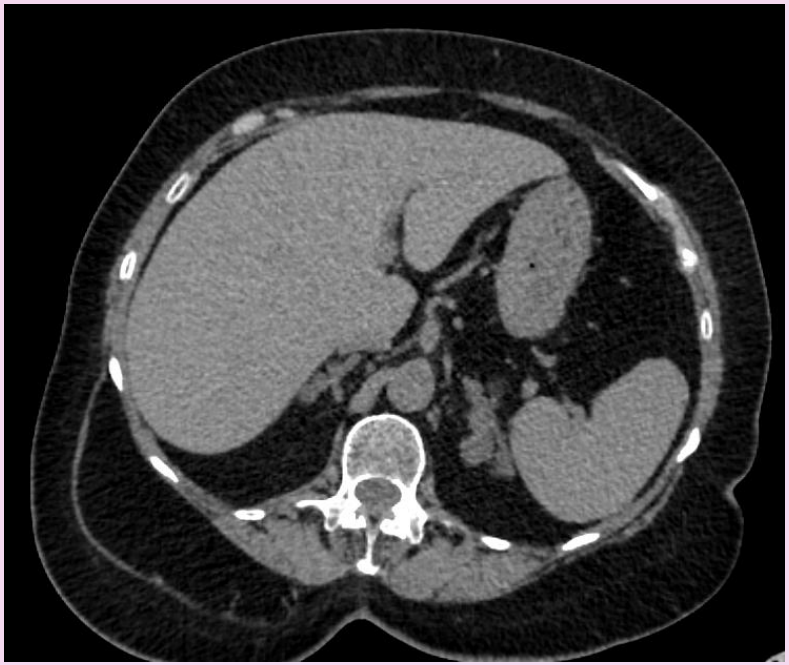


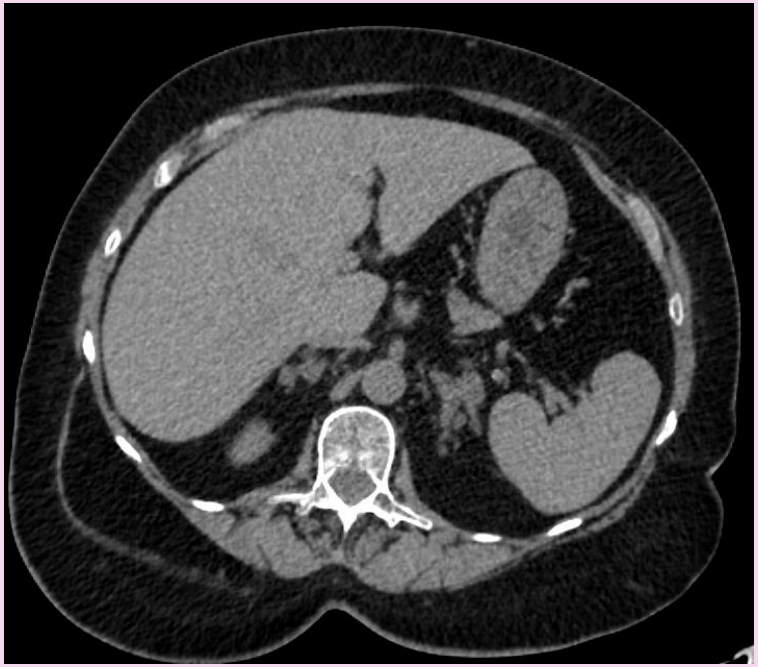


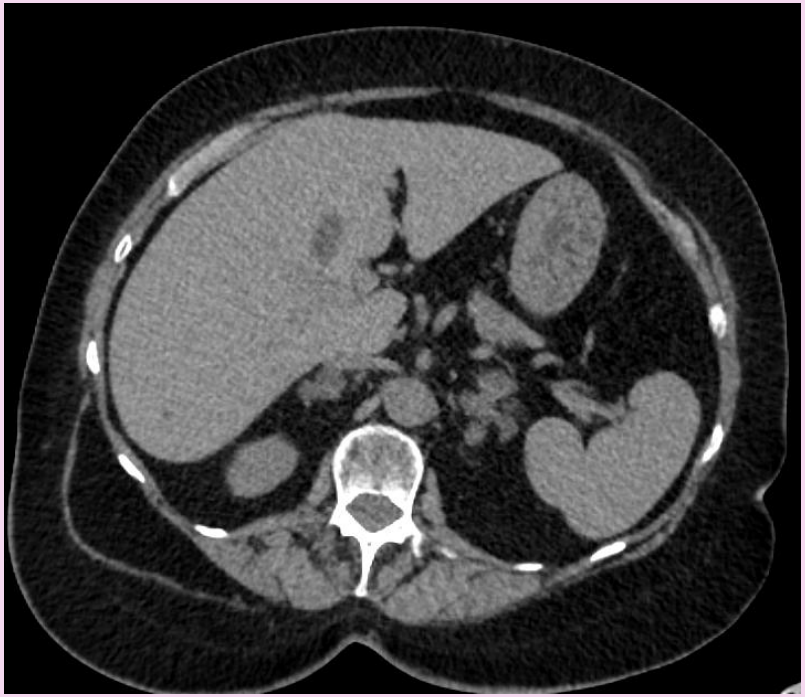


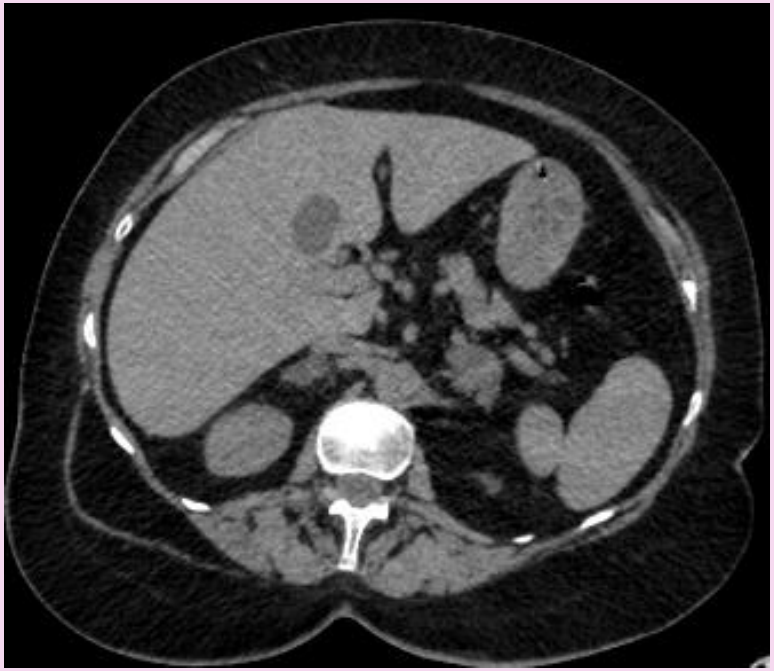


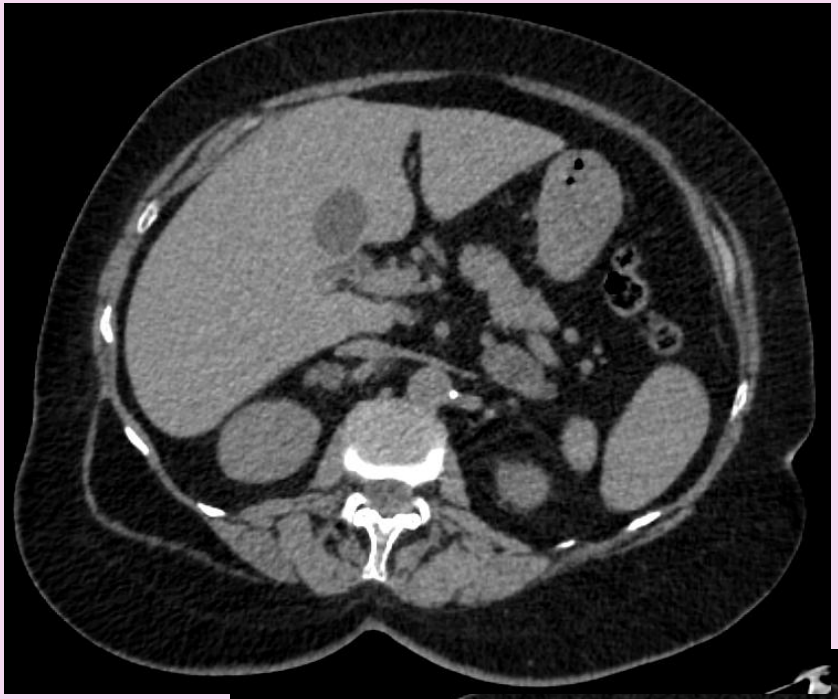


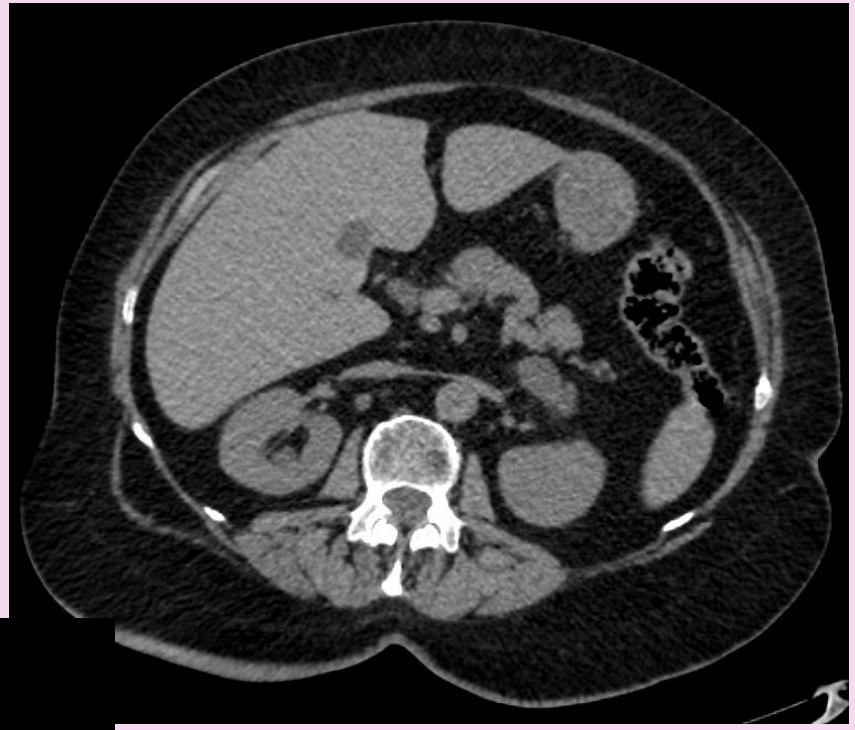


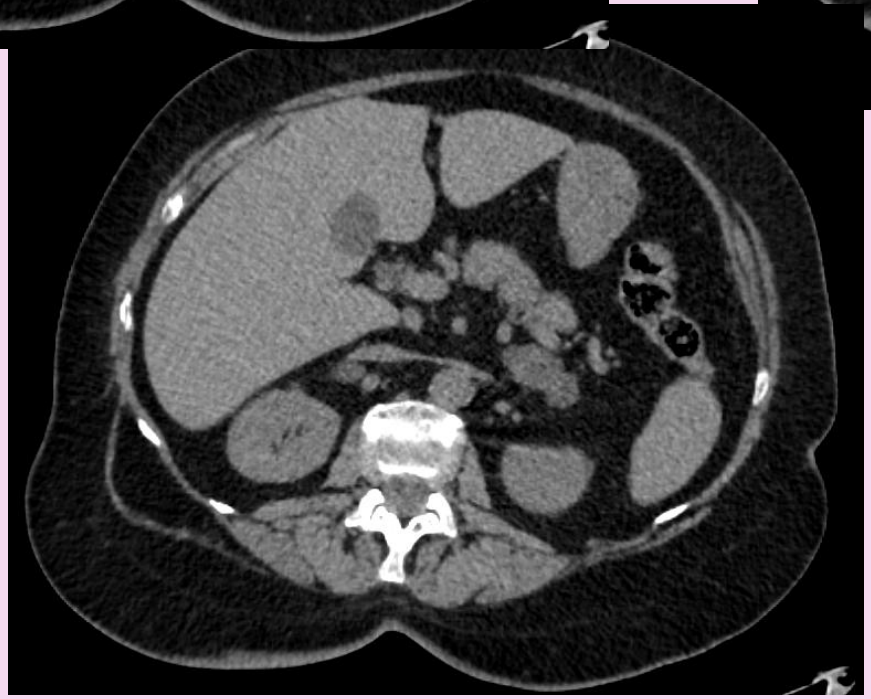












¿EVALUACIÓN DE FAMILIARES?

- No hay consenso (ni recomendaciones de expertos)
- Familiares de pacientes esporádicos
- Portadores de mutación ARMC5
  - Cortisol tras 1 mg DXM a los >25 años
  - ¿Con qué periodicidad?
  - Seguimiento radiológico “cauto”
- Formas familiares sin mutación ARMC5
  - Cortisol tras 1 mg DXM a los >25 años
  - TAC si cortisol >1,8 mcg/dl

TRATAMIENTO

- Suprarrenalectomía bilateral
- Suprarrenalectomía unilateral
- Tratamiento médico específico
  - Propranolol
  - Leuprolide
- Inhibidores de la esteroidogénesis, antagonistas de glucocorticoides

SUPRARRENALECTOMÍA UNILATERAL

	n	Remisión	Seguimiento sin recidiva (meses)	Recidiva (meses)	IS postQx
Lamas 2002	4	4/4	137 – 76 – 72 – 30	0/4	2/4
Iacobone 2008	7	6/7	53 (27-68)	0/6	2/7
Xu 2013	14	13/14	69 (23–120)	0/13	2/14
Albiger 2015	12	11/12	80 – 103 – 135	8/11 (54±56)	2/12
Debillon 2015	15	15/15	60 (IQR 39-105)	2/15 82 – 98	6/15 (3 no recup)
Osswald 2019	25	21/25		3/21	12/25 (2 no recup)

Lamas et al. Eur J Endocrinol 2002; 146:237-40
Xu et al. World J Surg 2013; 37:1626–32
Iacobone et al; World J Surg 2008; 32:882–9
Debillon et al. JCEM 2015; 100:4417–24
Albiger et al. Clin Endocrinol 2015; 82:808-15
Osswald et al. JCEM 2019; 104:2985-93

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE BRIEF REPORT

Propranolol Therapy for Ectopic β-Adrenergic Receptors in Adrenal Cushing's Syndrome

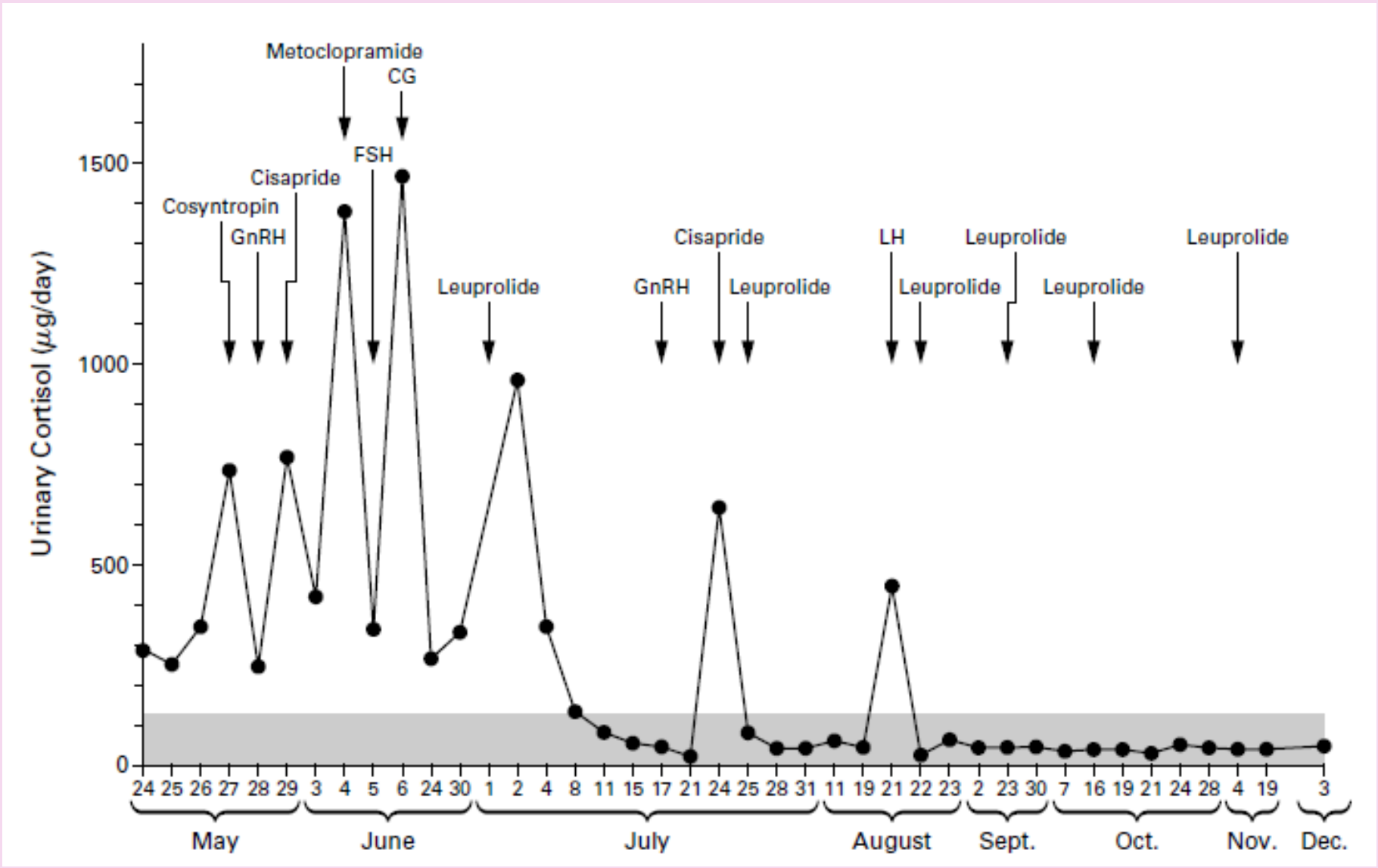
André Lacroix, M.D., Johanne Tremblay, Ph.D., Guy Rousseau, Ph.D., Michel Bouvier, Ph.D., and Pavel Hamet, M.D., Ph.D.

ORIGINAL ARTICLE BRIEF REPORT

Leuprolide Acetate Therapy in Luteinizing Hormone–Dependent Cushing's Syndrome

André Lacroix, M.D., Pavel Hamet, M.D., Ph.D., and Jean-Marie Boutin, M.D., Ph.D.

Lacroix et al. N Engl J Med. 1997;337(20):1429-34
Lacroix et al. N Engl J Med. 1999;341(21):1577-81


Urinary Cortisol (μg/day)
1500
1000
500
0
Metoclopramide
CG
FSH
Cisapride
Cosyntropin
GnRH
Leuprolide
Cisapride
GnRH
Leuprolide
LH
Leuprolide
Leuprolide
Leuprolide
Leuprolide
24 25 26 27 28 29 3 4 5 6 24 30 1 2 4 8 11 15 17 21 24 25 28 31 11 19 21 22 23 2 23 30 7 16 19 21 24 28 4 19 3
May
June
July
August
Sept.
Oct.
Nov.
Dec.

Clinical Study | I Bourdeau and others | *ARMC5* mutation in familial BMAH | 174:1 | 85–96

ARMC5 mutations in a large French-Canadian family with cortisol-secreting β-adrenergic/vasopressin responsive bilateral macronodular adrenal hyperplasia

Isabelle Bourdeau[1,2], Sylvie Oble[1], Fabien Magne[1], Isabelle Lévesque[1], Katia Y Cáceres-Gorriti[1], Serge Nolet[3], Philip Awadalla[4], Johanne Tremblay[1], Pavel Hamet[2], Maria Candida Barisson Villares Fragoso[5] and André Lacroix[1]

[1]Division of Endocrinology, Department of Medicine and [2]Division of Medical Genetics, Department of Medicine, Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, Quebec, Canada, [3]Department of Pathology, CHUM, Montréal, Quebec, Canada, [4]Department of Pediatrics, Centre de Recherche CHU Sainte-Justine, Université de Montréal, Montréal, Quebec, Canada and [5]Unidade de Suprarrenal, Disciplina de Endocrinologia e Metabologia, Laboratório de Hormônios e Genética Molecular LIM42, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil

Correspondence should be addressed to I Bourdeau
Email
isabelle.bourdeau@umontreal.ca

Bourdeau et al. Eur J Endocrinol 2016; 174(1):85-96

CLINICAL RESEARCH ARTICLE

Mifepristone Treatment in Four Cases of Primary Bilateral Macronodular Adrenal Hyperplasia (BMAH)

Pejman Cohan,[1] Honey E. East,[2] Sandi-Jo Galati,[3] Jennifer U. Mercado,[4] Precious J. Lim,[5] Michele Lamerson,[5] James J. Smith,[5] Anne L. Peters,[6] and Kevin C. J. Yuen[4,7]

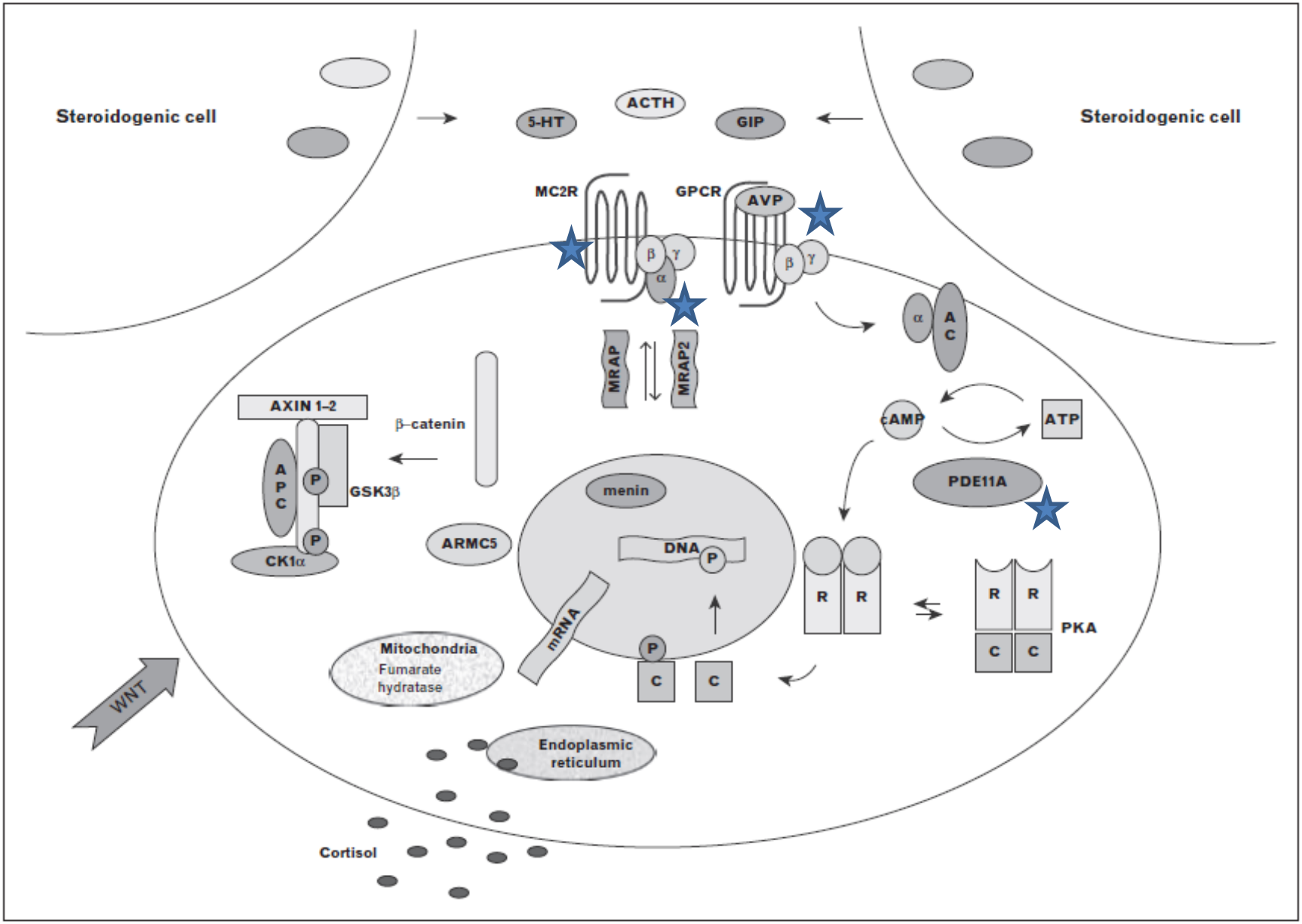
[1]Specialized Endocrine Care Center, Beverly Hills, California 90211; [2]Baptist Premier Medical Group, Jackson, Mississippi 39202; [3]Endocrine and Diabetes Specialists of Connecticut, Trumbull, Connecticut 06611; [4]Swedish Pituitary Center, Departments of Neuroendocrinology and Neurosurgery, Swedish Neuroscience Institute, Seattle, Washington 98122; [5]Corcept Therapeutics, Menlo Park, California 94025; [6]Keck School of Medicine, University of Southern California, Los Angeles, California 90033; and [7]Barrow Pituitary Center, Departments of Neuroendocrinology and Neurosurgery, Barrow Neurological Institute, University of Arizona College of Medicine, Phoenix, Arizona 85013

Cohan et al. JCEM 2019; 104: 6279–90

Table 3. Assessments Before and After Mifepristone Treatment

	Case 1		Case 2		Case 3		Case 4		
Duration of mifepristone treatment at data collection	4 mo		18 mo		3 mo		2 wk	6 mo	
Maximum dosage	300 mg 3 times/wk		600 mg once daily		300 mg once daily		600 mg once daily	900 mg once daily	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	
ACTH, pg/mL (normal 6–50 pg/mL)	<5	108	<5	54	<5	29	<1.1	<1.1	<5
Fasting plasma glucose, mg/dL (normal 65–99 mg/dL)	253	121	139	113	116	99	115	91	85
HbA1c, % (normal <5.7%)	8.1	6.7	8.5	5.7	6.1	5.8	6.3	—	—
Blood pressure, mm Hg (normal 120/80 mm Hg)	129/70	127/81	141/88	137/81	170/90	140/80 Patient has PA treated with spironolactone	156/104	122/94	98/62
Weight loss, kg	0		23.2		2.3			10.9	10
Side effects/intervention	Fatigue/none TSH increase/ levothyroxine		Gastrointestinal discomfort/ reduction in mifepristone dosage Fatigue/none Hypokalemia/ spironolactone dosage increase		Heat intolerance/none		Fatigue, nausea, headache/ none TSH increase/levothyroxine		
Clinical outcomes	Reduction in HbA1c despite complete liberalization of diet		Resolution of diabetes with discontinuation of insulin Decreased blood pressure with less medication		Reduction in blood pressure and HbA1c Improved anxiety, energy, sleep		Resolution of blood pressure and glucose parameters Palliation of Cushingoid features Improved sleep, energy, cognitive function, and mood		

¡MUCHAS GRACIAS POR VUESTRA ATENCIÓN!



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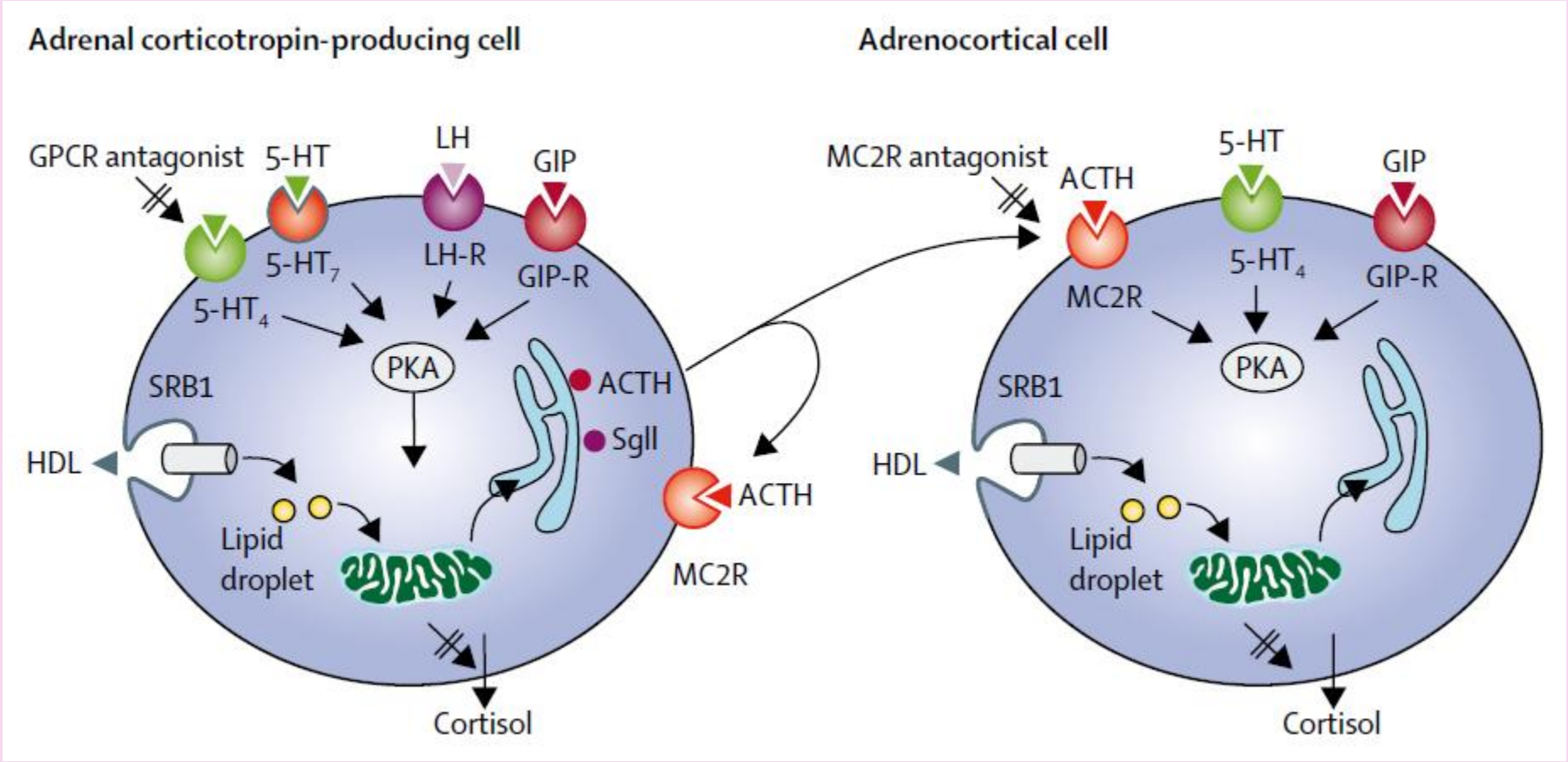
Adrenal corticotropin-producing cell
Adrenocortical cell
GPCR antagonist
5-HT
LH
GIP
5-HT7
LH-R
GIP-R
5-HT4
PKA
SRB1
ACTH
SgII
HDL
Lipid droplet
ACTH
MC2R
Cortisol
MC2R antagonist
ACTH
5-HT
GIP
5-HT4
MC2R
GIP-R
PKA
SRB1
HDL
Lipid droplet
Cortisol