



Desafios no diagnóstico da Síndrome de Cushing

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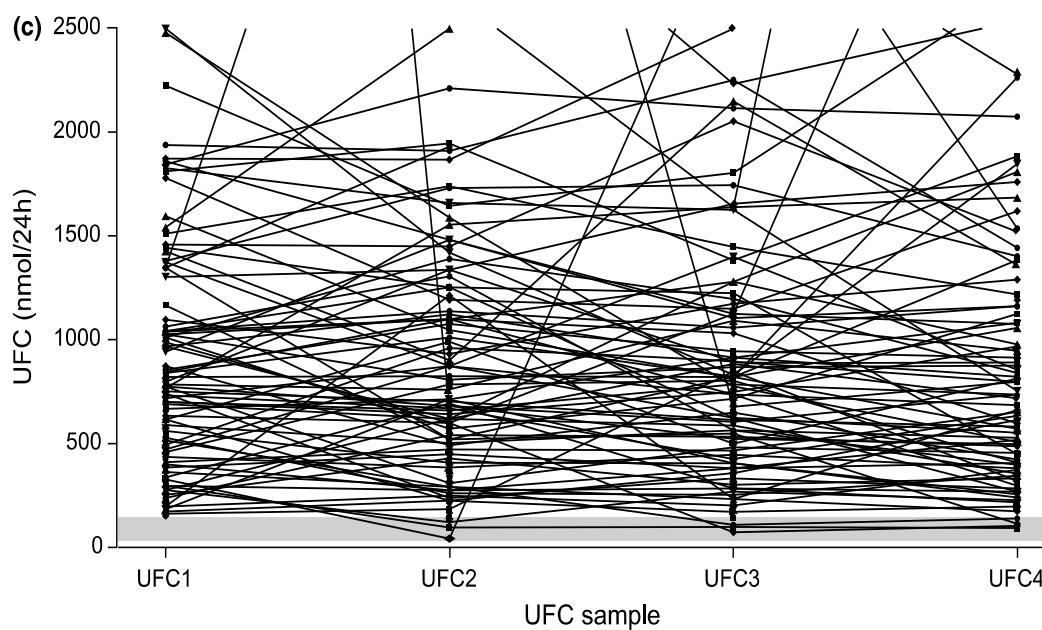
IPq HCFMUSP

- Sem conflitos de interesse

Diagnóstico Laboratorial de hipercortisolismo

- Aumento da concentração de cortisol na saliva 0 h
 - Aumento de excreção de cortisol urinário
 - Ausência de supressão do cortisol sérico sob dexametasona 1 mg (SN 2mg VO)
 - Perda do ritmo circadiano de cortisol
 - Cortisol sérico às 24 h > 7,5 µg/dL
- Sensibilidade: 94%*
- Especificidade: 100%*

DC: variabilidade dos níveis de cortisol livre urinário em 608 amostras de 152 pacientes



- The overall mean mUFC level \pm SD was $351 \pm 717 \mu\text{g}/24\text{h}$.
- The median mUFC level was $201 \mu\text{g}/24\text{h}$ range ($70 \pm 8315 \mu\text{g}/24\text{h}$).
- For the first two UFC samples collected from each patient, the mean \pm SD mUFC level was $362 \pm 679 \mu\text{g}/24\text{h}$ median $221 \mu\text{g}/24\text{h}$.
- For the second two UFC samples collected from each patient, the mean \pm SD mUFC level was $341 \pm 779 \mu\text{g}/24\text{h}$ median $191 \mu\text{g}/24\text{h}$.
- The mean baseline urinary creatinine level was $9.7 \pm 3.7 \text{ nmol}/24\text{h}$.
- The mean baseline urinary volume was $2123 \pm 914 \text{ mL}/24\text{h}$.
 - Eight patients had ≥ 1 UFC value in the normal range
 - Three patients had 2 UFC values in the normal range
 - One patient had 3 UFC values in the normal range and medication was started after the first collection
- The variability in UFC levels increased as UFC levels increased.

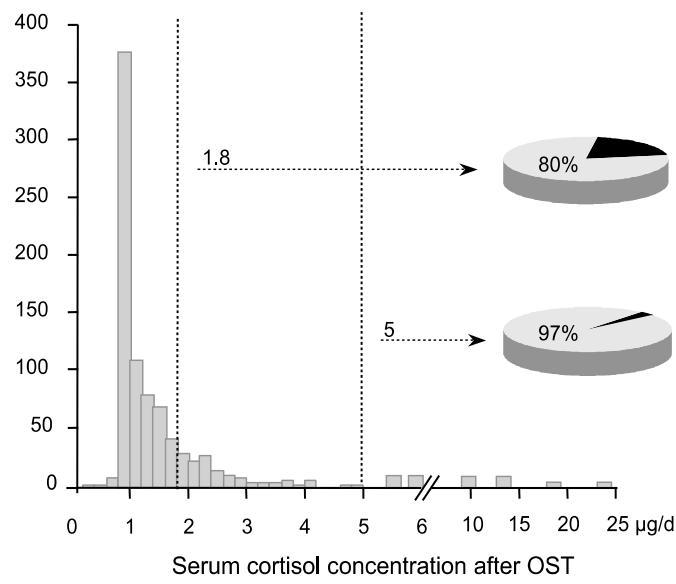
UFC was measured in duplicate by high performance liquid chromatography (HPLC), as described in Turpeinen et al 1997; range for this assay is $\sim 11\text{--}53 \mu\text{g}/24\text{h}$

Variabilidade dos níveis de cortisol livre urinário

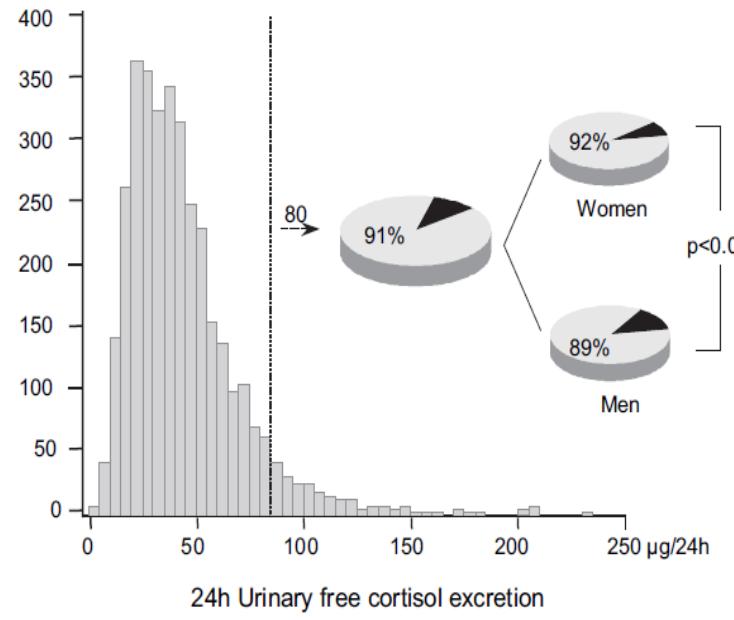
- There was minimal correlation between baseline mUFC levels and baseline fasting glucose, HbA_{1c}, fasting insulin, insulin resistance, β-cell function, BMI, or systolic/diastolic blood pressure.
- Two-sample UFC measurement yields a reasonable estimate of within-patient variation but more precise estimates can be obtained with three to four UFC measures.
- There was a wide variability in UFC measurements over a short period of time within individual patients (52%).
- **Reductions in UFC from baseline should be >50% for an intervention effect to be considered beyond the normal variability of UFC.**

Dexa 1mg, cortisol livre urinário e cortisol à meia noite (N=4126)

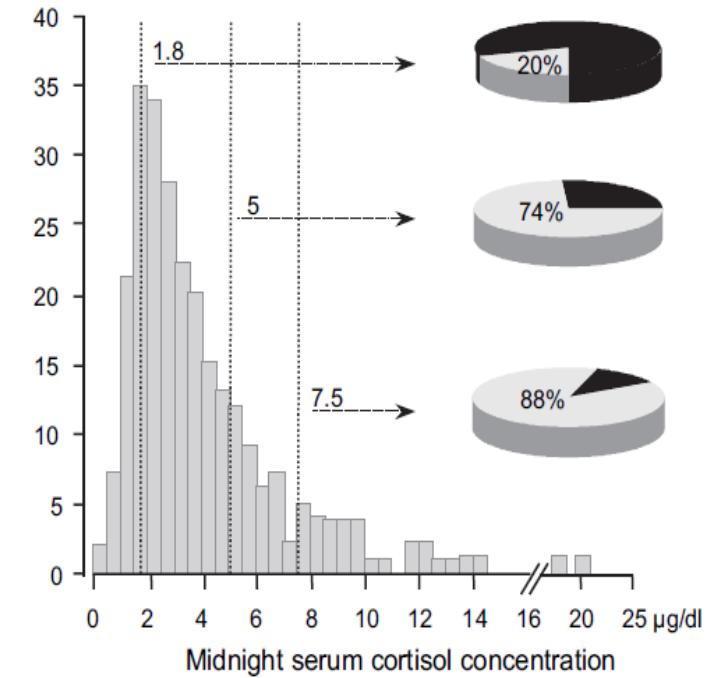
N: 864



N: 3461



N: 357



Pecori-Giraldi, 2007

Diagnóstico de hipercortisolismo: lembrar!!

- ACO e gravidez: não realizar 1mg DST;
- Epilepsia: não realizar DST → dextroepoxibuprofeno é metabolizada por drogas anti-epiléticas;
- IRC: não utilizar cortisol urinário para diagnóstico;
- IRC: pode haver aumento do F salivar;
- Síndrome de Cushing cíclica: usar cortisol urinário ou salivar;
- Cortisol urinário: **falso positivo** qdo o vol urinário >5 litros;
- HPLC: **falso positivo** qdo em uso de digoxina, carbamazepina e fenofibrato.

Pseudo-Cushing X Síndrome de Cushing

- Alcoolismo
- Depressão
- Obesidade
- Síndrome metabólica
- Apneia Obstrutiva do Sono
- SOP



oCRH pós 2 mg dextroresina:
Fs > 1,4 µg/dL (15')

DDAVP® pós 2 mg dextroresina:
Fs > 2,7 µg/dL (15')

DDAVP:
ACTH ≥ 27 pg/ml
ACTH ≥ 18 pg/ml

oCRH pós 2 mg dextroresina:
Fs > 2,5 µg/dL (15')

oCRH pós 2 mg dextroresina:
Fs > 3,8 µg/dL (15')



Síndrome de
Cushing

Yanovski, 1993
Salgado, 1998
Moro, 2000
Erickson, 2007
Gatta, 2007

Teste do CRH-dexametasona

Variáveis limitantes:

1. Metabolismo da dexametasona (pela CYP3A4): tabagismo, álcool, carbamazepina, nifedipina, fenobarbital, fenitoína, rifampicina, St. John's wort, tamoxifeno e topiramato.
 - ***Medida dos níveis séricos de dexametasona é vital !!!***
2. Linha de corte do cortisol é variável dependendo do ensaio:
 - 1,4 µg/dL (Yanovski, 1993)
 - 1,5-1,8µg/dL (Martin, 2006)
 - 2,5 µg/dL (Erikson, 2007)
 - 3,8 µg/dL (Gatta, 2007)
3. Utilizando-se linhas de corte maiores, a performance do teste é melhor!

Síndrome de Cushing ACTH-independente

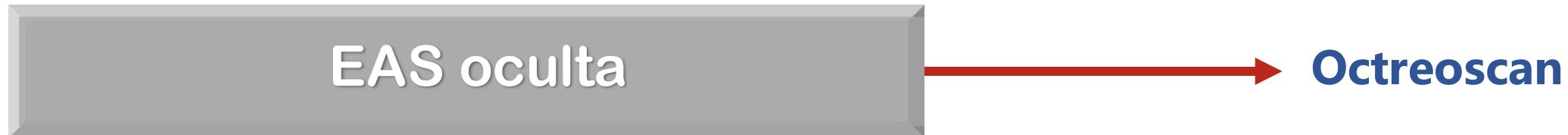
- Iatrogênica
- Tumores adrenais
 - Adenomas
 - Carcinomas
- Causas Incomuns
 - PPNAD (Complexo de Carney)
 - Hiperplasia adrenal macronodular independente de ACTH (AIMAH)
 - Receptores ilícitos (ectópicos)
 - Vasopressina (V_1), Serotonina ($5-HT_4$), GIP, LH / hCG, β -adrenérgico, Angiotensina II (AT_1).

Síndrome de Cushing ACTH-dependente

- Hiperplasia adrenal nodular bilateral
- Adenomas hipofisários (doença de Cushing)
- Neoplasias ectópicas (EAS)
 - Aparentes
 - Ocultas

Diagnóstico diferencial SC ACTH-dependente

- Níveis de ACTH
- Testes dinâmicos
- Cateterismo bilateral e simultâneo dos seios petrosos inferiores (IPSS)



Teste do CRH ovino

	<i>Sensitivity</i>	<i>Specificity</i>
ACTH > 35%	93%	100%
Cortisol > 20%	88%	91%

Nieman, 1993

Teste de supressão com dexametasona 8mg

	Supressão (%)	Não-supressão (%)
Doença de Cushing	<i>60-70%</i>	<i>20-30%</i>
EAS	<i>20-30%</i>	<i>60-70%</i>

Accuracy: 70-80%

Pre-test probability: 85-90%

HC-FMUSP / HB

Intervalo

= 0-95%

Média \pm EP

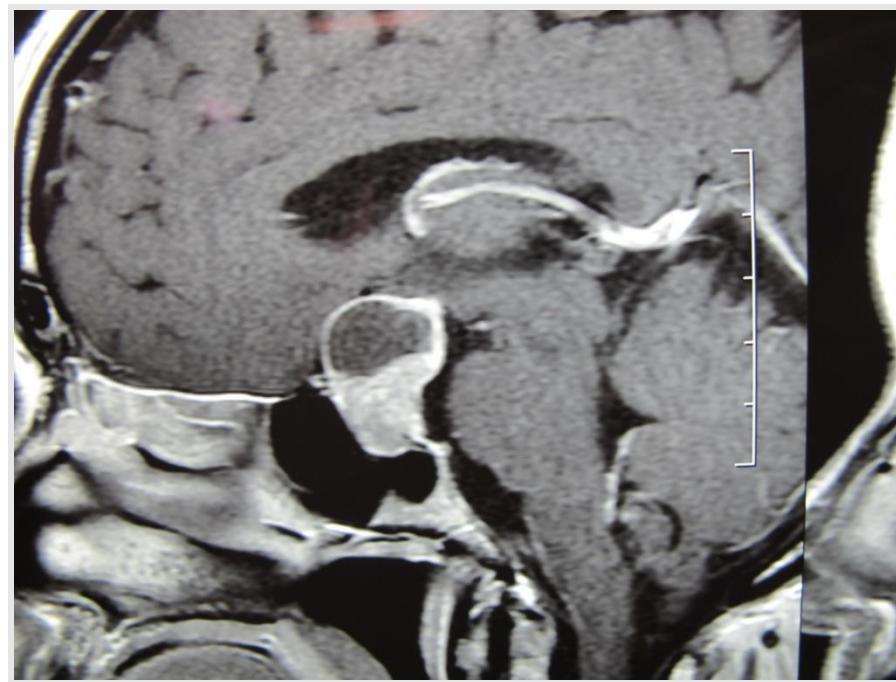
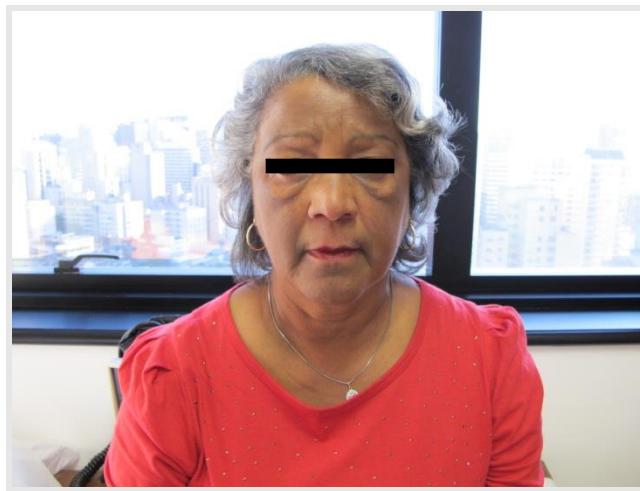
= $65,3 \pm 4,2\%$

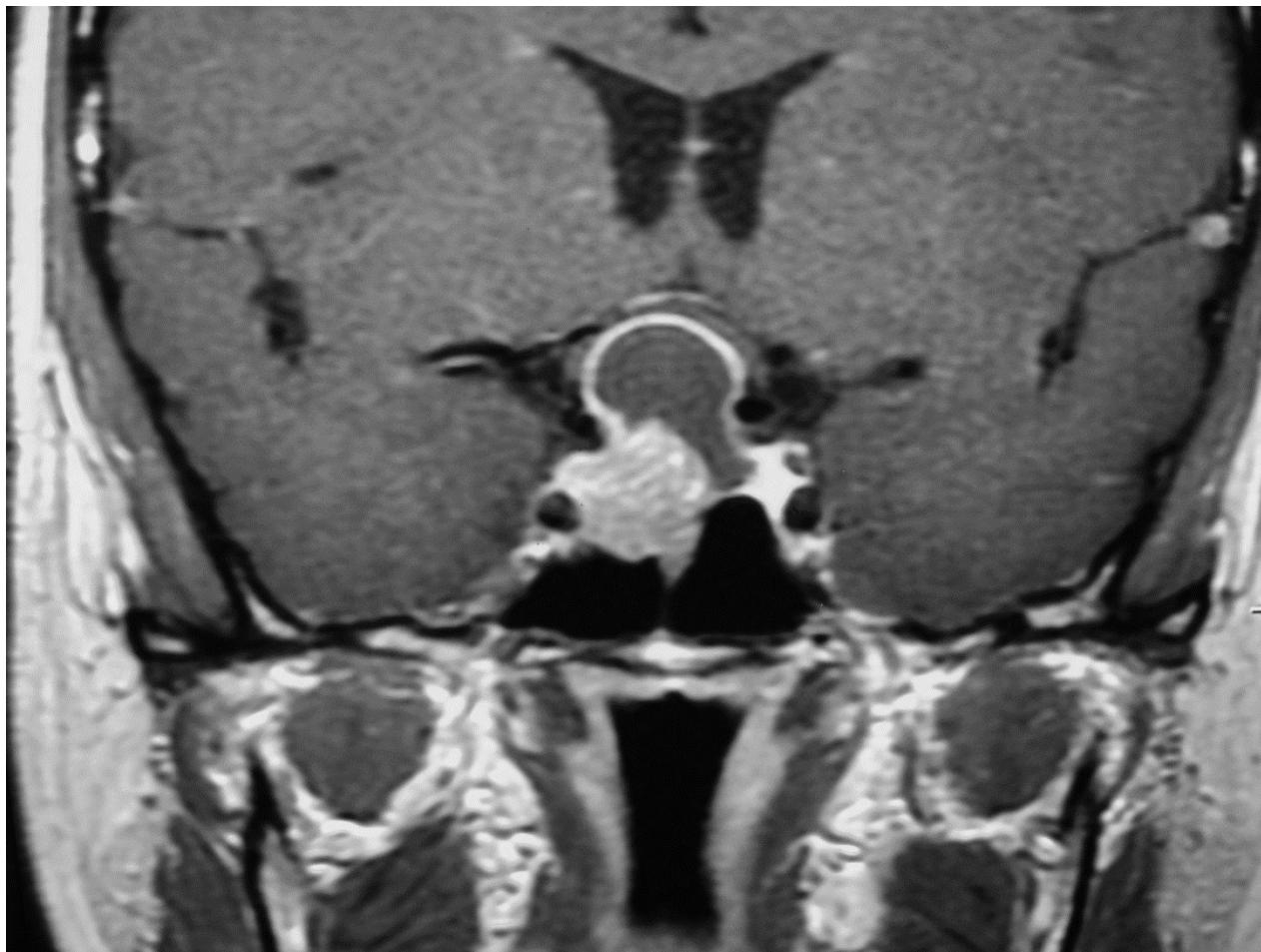
Mediana

= 70%

positivo $\begin{cases} \geq 50\% & = 81,0\% \\ \geq 70\% & = 51,5\% \end{cases}$

ACTH elevado e síndrome metabólica leve

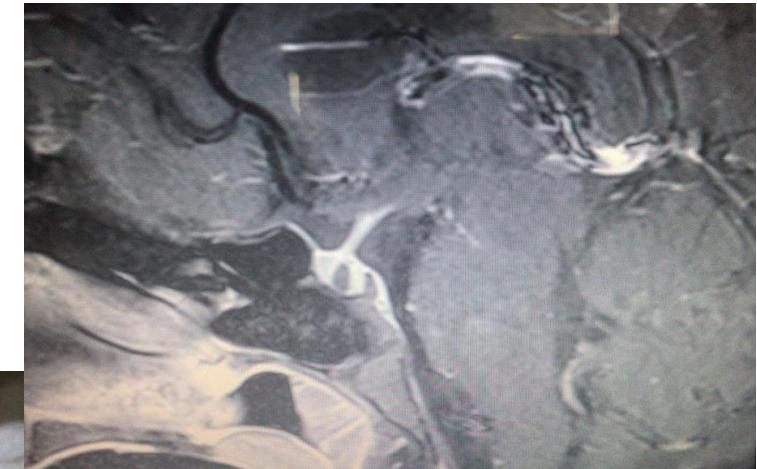
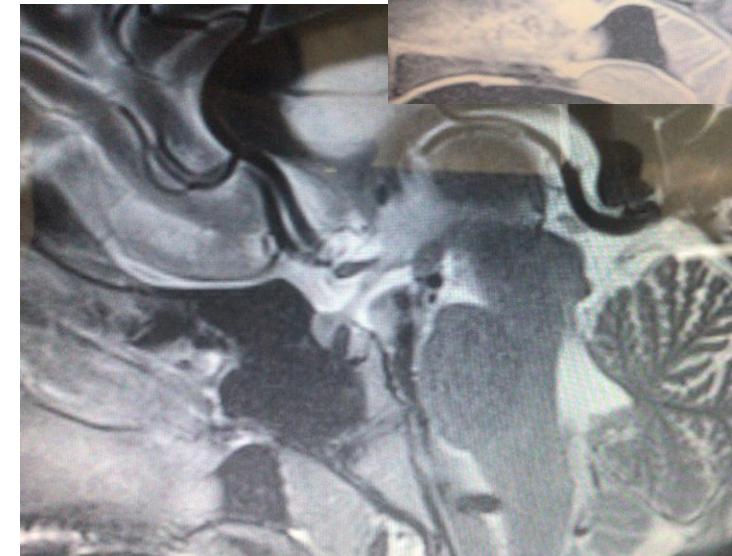




Ressonância intra-operatória

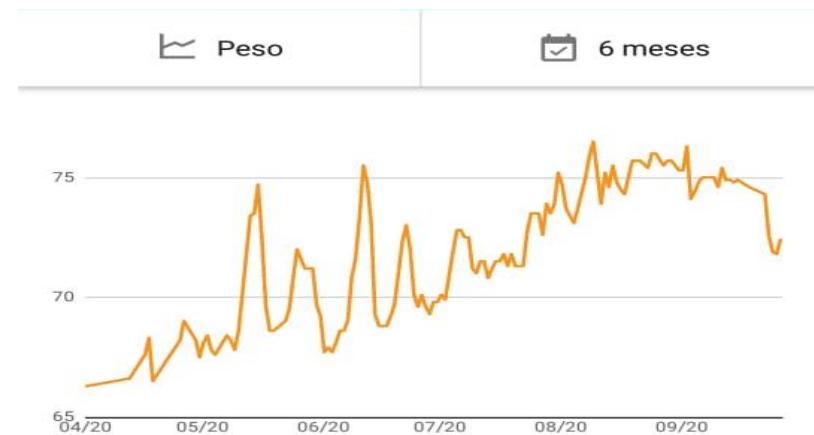


8a, "crises convulsivas", HAS, estigmas típicos de Cushing, cefaleia, dores no corpo.



Caso Clínico 2:

41a, ganho de peso centrípeto intermitente, herpes cutâneo, edema generalizado (julho/18), sem HAS ou DM, apresenta redução de força, hirsutismo e acne.



Data	03/07/18	01/08/18	14/08/18	15/08/18	22/09/18 (Cate SPIs)
Fu (<43)	1748		628		20,7
F sal 24h (<100)		406	1822		
F pós Dexa 8mg				2,6	
ACTH (< 46)	42		57		30
F			8,1		7,0



Internação julho/18



Octreoscan (30/08/2018) e cateterismo de seios petrosos inferiores (21/09/2018)

**PESQUISA DE CORPO INTEIRO
COM ANÁLOGOS DA SOMATOSTATINA**

Radiotármaco: DOTATATE-68 Ga

Técnica: cortes tomográficos (PET) acoplado a tomógrafo "multislice", fusão de imagens metabólicas e morfológicas (PET-CT)

Indicação clínica: investigação de síndrome de Cushing

RELATÓRIO:

Os cortes tomográficos (PET) e as imagens de fusão com cortes anatômicos (TC) revelam nódulo de 1,0 cm no vértice da adenal esquerda com concentração normal do tránsito, indeterminado.

Demais segmentos avaliados demonstram distribuição usual do indicador com predominância de concentração na hipófise, tireoide, glândulas salivares, fígado, adrenal direita, baço e excreção através de vias urinárias e de alças intestinais.

Achados adicionais da tomografia computadorizada sem alteração correspondente nas imagens funcionais:

- sinais de hiperostose frontal benigna;
- útero dimensões aumentadas, contornos lobulados;
- ilhota óssea no ilíaco esquerdo.

INTERPRETAÇÃO:

Estudo sem evidências de áreas com significativo acúmulo do indicador sugestivas de lesões com expressão anômala de receptores de somatostatina.

Nódulo indeterminado na adrenal esquerda.

Relatado por: Dr. Marcelo Livorsi da Cunha - CRM 66209

Relatado por: Dra. Thais Caldara Mussi de Andrade - CRM 123439

Revisado e Assinado Eletronicamente por: Dr. Marcelo Livorsi da Cunha - CRM 66209

HORMONIO ADRENOCORTICOTROFICO (ACTH), plasma

Método: Ensaio imunométrico quimioluminescente

LOCAL/TEMPO	ACTH (pg/mL) SEIO PETROSO DIREITO	ACTH (pg/mL) SEIO PETROSO ESQUERDO	ACTH (pg/mL) PERIFÉRICO
Basal	411	221	113
3 min	749	434	97
5 min	420	248	95
10 min	424	207	84

LOCAL/TEMPO	PRL (pg/mL) SEIO PETROSO DIREITO	PRL (pg/mL) SEIO PETROSO ESQUERDO	PRL (pg/mL) PERIFÉRICO
Basal	110	31	21

$$\text{PRL: SPD/P} = 110/21 = 5,2 \text{ (cateter bem locado} > 1,8)$$

$$\text{Gradiente de ACTH corrigido pelo de PRL: } \frac{749}{97} = 1,48 \\ 110/21$$

Cushing hipofisário $> 1,3$ e ectópico $< 0,7$

Cyclic Cushing's disease with misleading inferior petrosal sinus sampling results during a trough phase

Vivien Bonert, MD,¹ Namrata Bose, MD,² and John D. Carmichael, MD²

¹Pituitary Center, Cedars-Sinai Medical Center; and ²USC Pituitary Center, Keck School of Medicine of University of Southern California, Los Angeles, California

TABLE 1. Initial IPSS

Specimen Time (mins)	Petrosal ACTH (pg/ml)		Peripheral ACTH (pg/ml)
	Lt	Rt	
-5	28	28	30
0	27	28	29
3	28	28	27
5	75	91	46
10	123	125	93
Jugular Vein (pg/ml)			
Lt		Rt	
15	485	118	101
Superior Vena Cava (pg/ml)			
17	109		97
Inferior Vena Cava Supra-adrenal (pg/ml)			
19	112		99
Inferior Vena Cava Infra-adrenal (pg/ml)			
20	102		115

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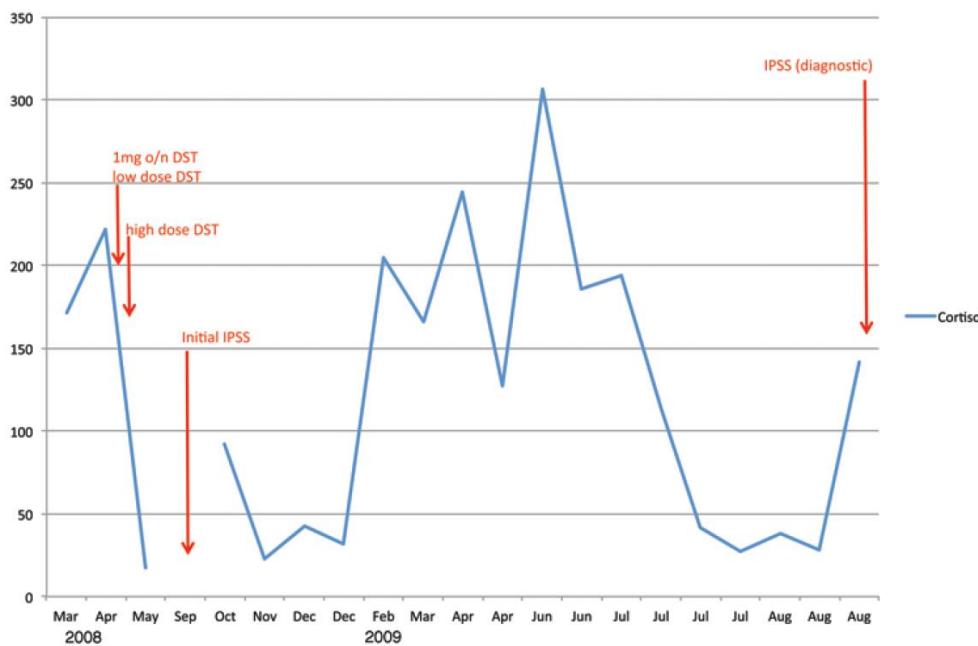


FIG. 1. Laboratory evaluation of serial measurements of 24-hour UFC levels revealed 3 distinct peaks and 2 trough periods. Collections for 24-hour UFC were often obtained multiple times per month. Dexamethasone suppression testing and IPSS are indicated by the arrows. o/n DST = overnight dexamethasone suppression test.

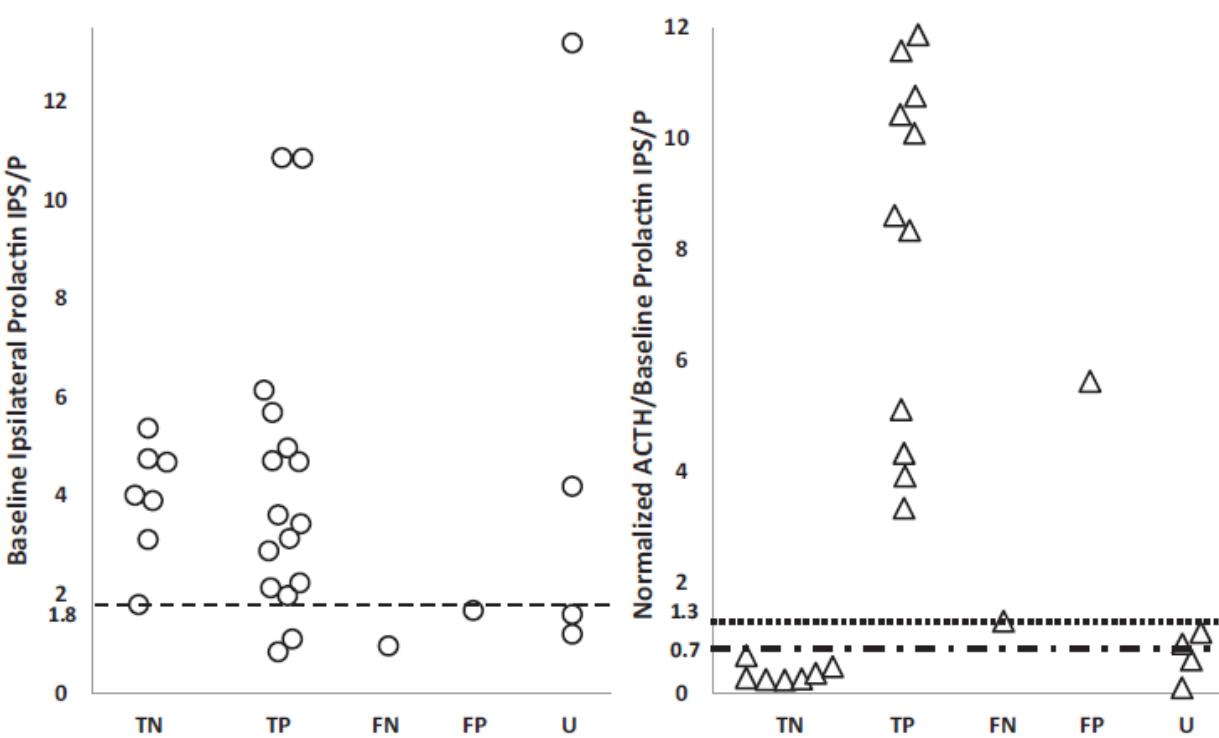
TABLE 2. Diagnostic IPSS

Specimen Time (mins)	Petrosal ACTH (pg/ml)		Peripheral ACTH (pg/ml)
	Lt	Rt	
-5	34	34	32
0	31	30	27
3	515	652	27
5	579	1395	78
10	233	243	216
Jugular Vein (pg/ml)			
15	504	243	166
Superior Vena Cava (pg/ml)			
17	240	196	
Inferior Vena Cava Supra-adrenal (pg/ml)			
19	208	181	
Inferior Vena Cava Infra-adrenal (pg/ml)			
20	174	143	

Prolactin as a Marker of Successful Catheterization during IPSS in Patients with ACTH-Dependent Cushing's Syndrome

S. T. Sharma, H. Raff, and L. K. Nieman

FIG. 1. Baseline ipsilateral prolactin IPS/P ratios (left panel) and normalized ACTH/prolactin IPS/P ratios (right panel) in 29 patients with ACTH-dependent Cushing's syndrome (25 with a surgically proven diagnosis and four with occult Cushing's syndrome). Patients were divided into true negatives (TN: pathology and IPSS results consistent with EAS, n = 7), true positives (TP: pathology and IPSS results consistent with CD, n = 16), false negatives (FN: negative IPSS results in a patient with surgically proven CD, n = 1), false positive (FP: positive IPSS results in a patient with surgically proven EAS, n = 1), and occult (U: biochemical testing consistent with EAS, but a source could not be localized). Normalized ACTH/prolactin IPS/P ratios in five cases were higher than 12 and are not shown in the above figure. All patients with surgically proven Cushing's disease had a normalized ACTH IPS/P ratio of 1.3 or higher (dotted line). Patients with surgically proven EAS (except for the false-positive case) had a normalized ACTH/prolactin IPS/P ratio of 0.7 or lower (dashed line). CD, Cushing's disease.



Prolactin as a Marker of Successful Catheterization during IPSS in Patients with ACTH-Dependent Cushing's Syndrome

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TABLE 1. Clinical features of two patients with erroneous IPSS results (false negative and false positive)

Characteristic	False negative (IPSS, ectopic; pathology, CD)	False positive (IPSS, CD; pathology, ectopic)
Age at diagnosis (yr)	23	54
Sex	Male	Female
Symptoms/signs	Weight gain, facial swelling, muscle weakness, violaceous striae, easy bruising, dorsocervical and supraclavicular fat pads	Weight gain, proximal muscle weakness, easy bruising, memory problems, dorsocervical and supraclavicular fat pads
ACTH (pg/ml) (normal, <46)	65.7	34.5
24-h UFC ($\mu\text{g}/24\text{ h}$) (normal, 3.5–45)	3030	27 (eucortisolemic) 755 (hypercortisolemic)
CRH stimulation test results suggest	Pituitary	Ectopic (hypercortisolemic)
HD DST results suggest	Ectopic	Ectopic (hypercortisolemic)
MRI pituitary	7 mm left pituitary adenoma	Normal
IPSS		
Peak ACTH IPS/P ^a	1.3 (347/275)	9.5 (212/22.4)
Baseline PRL IPS/P ^a	1.0 (14.8/15.4)	1.7 (4.2/2.5)
ACTH/PRL IPS/P	1.3	5.6
Surgical pathology	Left 7-mm pituitary adenoma, staining positive for ACTH	Left lower pulmonary carcinoid, staining positive for ACTH

To convert ACTH level to picomoles per liter, multiply by 0.2202. To convert 24-h UFC level to nanomoles per day, multiply by 2.759. CD, Cushing's disease; HD DST, high-dose dexamethasone suppression test; PRL, prolactin; ectopic, ectopic ACTH secretion.

^a Actual ACTH or prolactin values are shown in parentheses.

Cirurgia TS, Dr Gilberto Ochman
em 08/10/18.



Caso Clínico 2:

Teste do DDAVP (22/10/2018), 14 dias após a cirurgia.
Qual é o critério de cura de Cushing cíclico?

ACTH APOS ESTIMULO COM DDAVP, plasma

Método: Ensaio eletroquimioluminométrico

Estímulo após 10 ug de DDAVP

RESULTADO	AMOSTRA
19 pg/mL	Basal
24 pg/mL	15 min
22 pg/mL	30 min
22 pg/mL	45 min
20 pg/mL	60 min
18 pg/mL	90 min

VALORES DE REFERÊNCIA: (para condições basais)
7 a 63 pg/mL entre 7 e 10 horas.

CORTISOL APOS ESTIMULO COM DDAVP, soro

Método: Imunoensaio competitivo por eletroquimioluminescência

Estímulo após 10 ug de DDAVP

RESULTADO	AMOSTRA
8,4 microg/dL	Basal
7,8 microg/dL	15 min
7,9 microg/dL	30 min
6,9 microg/dL	45 min
7,1 microg/dL	60 min
6,0 microg/dL	90 min

VALORES DE REFERÊNCIA: (para condições basais)
Entre 7 e 9 h: 6,0 a 18,4 microg/dL
Incremento de 20% do valor basal

Agradecimentos



“Quem sabe faz, quem não sabe, ensina”

Equipes IPq:

Neuroendocrinologia:

Dra. Nina Rosa

Dr. André Faria

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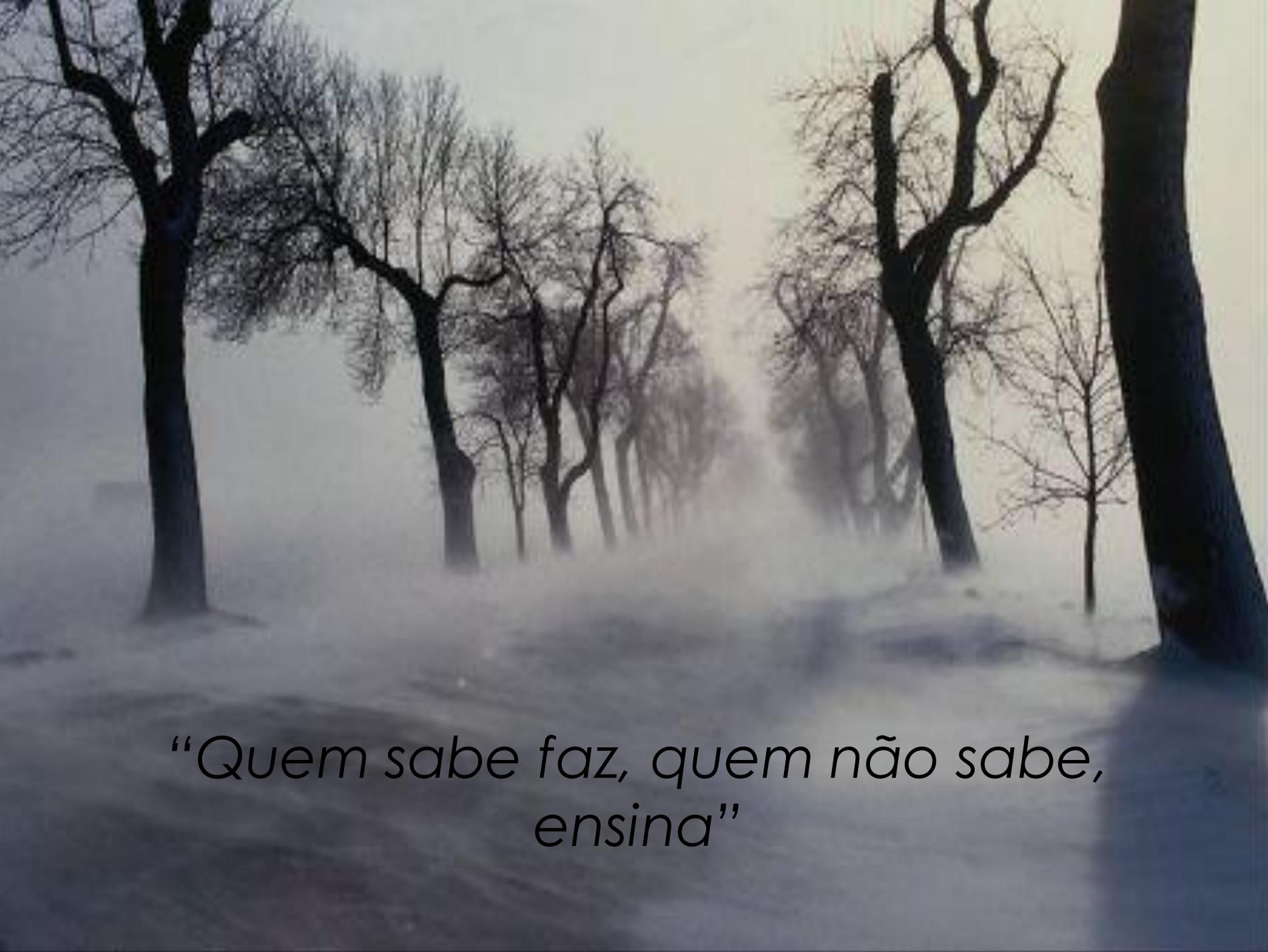
(cumprimento especial aos de Santa Catarina)

Neurocirurgia:

Dr. Gilberto Ochman

Dr. Valter Cescato

Residentes Neurocirurgia



*“Quem sabe faz, quem não sabe,
ensina”*