



## Retos en el diagnóstico y tratamiento de enfermedad de Cushing

Dr. Chih Hao Chen Ku, FACE  
Servicio de Endocrinología, Hospital San Juan de Dios  
Departamento de Farmacología y Toxicología Clínica,  
Universidad de Costa Rica

EndoDrChen.com

---

---

---

---

---

---

---

---

## Conflictos de interés

- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk
- Investigación clínica: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche

EndoDrChen.com

---

---

---

---

---

---

---

---

## Agenda

- Enfermedad de Cushing
  - Retos diagnósticos
  - Métodos diagnósticos en Centro América
  - Limitantes en tratamiento

EndoDrChen.com

---

---

---

---

---

---

---

---

# RETOS DIAGNÓSTICOS

EndoDrChen.com

---

---

---

---

---

---

---

---

## Introducción

- Muchas de las características del síndrome de Cushing se confunden con condiciones más comunes, como el síndrome metabólico
- España
  - Incidencia 2.4 casos por millón
  - Prevalencia 39.1 casos por millón
  - Aumento linear desde 1974 hasta 1992

EndoDrChen.com  
Steffensen C. Neuroendocrinology. 2010;92(Supl 1):1

---

---

---

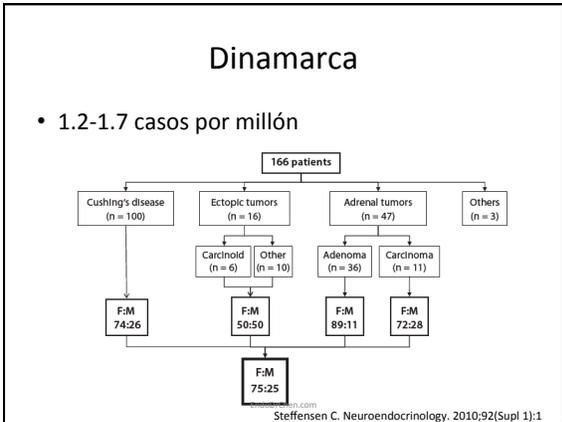
---

---

---

---

---




---

---

---

---

---

---

---

---



Symptoms	Signs	Overlapping conditions
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	Easy bruising Facial plethora Proximal myopathy (or proximal muscle weakness) Striae (especially if reddish purple and > 1 cm wide) In children, weight gain with decreasing growth velocity	
Cushing's syndrome features in the general population that are common and/or less discriminatory		
Depression Fatigue Weight gain Back pain Changes in appetite Decreased concentration Decreased libido Impaired memory (especially short term) Insomnia Irritability Menstrual abnormalities In children, slow growth	Hypertension <sup>o</sup> Dorsocervical fat pad ("buffalo hump") Facial fullness Obesity Supradavicular fullness Thin skin <sup>o</sup> Peripheral edema Acne Hirsutism or female balding Poor skin healing In children, abnormal genital virilization In children, short stature In children, pseudoprecocious puberty or delayed puberty	Hypertension <sup>o</sup> Incidental adrenal mass Vertebral osteoporosis <sup>o</sup> Polycystic ovary syndrome Type 2 diabetes <sup>o</sup> Hypokalemia Kidney stones Unusual infections
<small>EndoDrChen.com</small> Nieman LK. J Clin Endocrinol Metab. 2008;93:1526		

---

---

---

---

---

---

---

---

---

---

## Tamizaje

- Cortisoluria 24 horas
- Test supresión 1 mg dexametasona
- Cortisol salival a medianoche

EndoDrChen.com

---

---

---

---

---

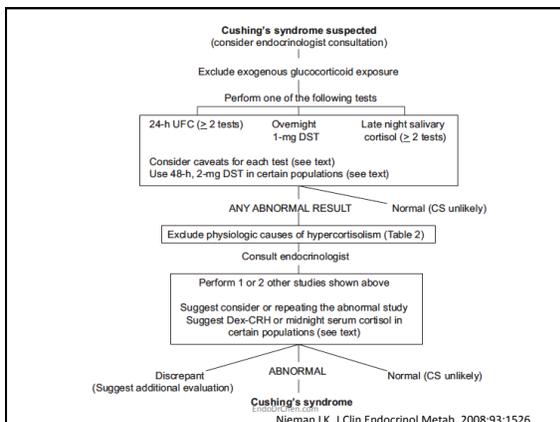
---

---

---

---

---




---

---

---

---

---

---

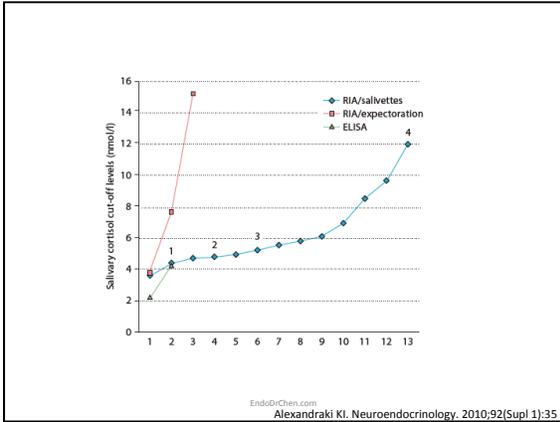
---

---

---

---






---

---

---

---

---

---

---

---

---

---

### Cortisol salival

- Estudios no han mostrado diferencias en cortisol salival hora sueño, 11 PM ó medianoche
- La sensibilidad no depende de un nivel de corte específico para toda la población
- Se debe determinar cuál es el nivel de corte para cada población y metodología utilizada

EndoDrChen.com  
Alexandraki KI. Neuroendocrinology. 2010;92(Supl 1):35.

---

---

---

---

---

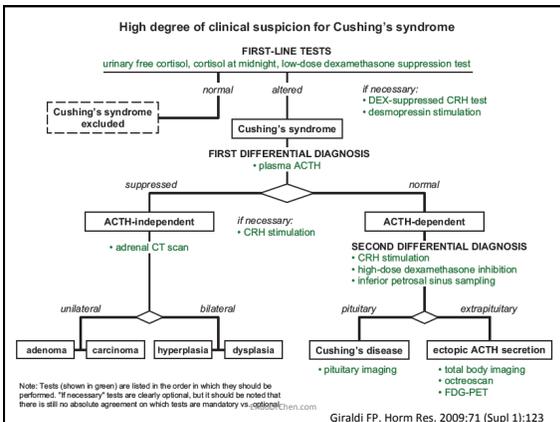
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

**TRATAMIENTO**

EndoOrChen.com

---

---

---

---

---

---

---

---

**Indicaciones**

Type of Cushing's syndrome	Indication
Pituitary-dependent Cushing's syndrome	Pretreatment before pituitary surgery Acute complications of hypercortisolism Persistent hypercortisolism after pituitary surgery Nonvisible adenomas High operation risk
Ectopic ACTH syndrome	Acute complications of hypercortisolism Unresectable or metastasized tumors High operation risk
Adrenal Cushing's syndrome	Acute complications of hypercortisolism Unresectable or metastasized adrenal carcinoma Ectopic hormone receptor expression High operation risk

Felders R. Neuroendocrinology. 2010;92(Supl 1):111

---

---

---

---

---

---

---

---

**Agentes bloqueadores de función adrenal**

- Mitotano
- Etomidato
- Metyrapone
- Ketoconazole

EndoOrChen.com  
Felders R. Neuroendocrinology. 2010;92(Supl 1):111

---

---

---

---

---

---

---

---

## Ketoconazol

- Altas dosis inhibe múltiples vías de esteroidogénesis:
  - 11 beta hidroxilasa
  - 17 hidroxilasa
  - 18 hidroxilasa
- 400-1200 mg por día
- Puede causar hipogonadismo en hombres

EndoOrChen.com  
Felders R. Neuroendocrinology. 2010;92(Supl 1):111

---

---

---

---

---

---

---

---

---

---

The screenshot shows the FDA website with a search bar and navigation tabs for Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. The main content area is titled "FDA Drug Safety Communication: FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems in Espanol". It includes a "Safety Announcement" section with a date of 7/26/2013 and a "Liver Injury (Hepatotoxicity)" section.

EndoOrChen.com

---

---

---

---

---

---

---

---

---

---

The screenshot shows the European Medicines Agency logo and a press release dated 26 July 2013 (EMA/458028/2013). The headline reads: "European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole. Benefit of oral ketoconazole does not outweigh risk of liver injury in fungal infections".

EndoOrChen.com

---

---

---

---

---

---

---

---

---

---

### Ketoconazole

- No hay estudios aleatorizados
- Algunos estudios retrospectivos muestran tasas de curación de 50-70%
- En modelos animales, logran suprimir producción de ACTH, efecto que se logra potenciar con el uso de pasireotide

EndoOrChen.com  
Felders R. Neuroendocrinology. 2010;92(Supl 1):111

---

---

---

---

---

---

---

### BLOQUEADORES RECEPTORES DE GLUCOCORTICOIDES

EndoOrChen.com

---

---

---

---

---

---

---

### Mifepristone

- 10x más afin por el receptor GC comparado con el cortisol
- Se une al receptor de progesterona y andrógenos

EndoOrChen.com  
Castinetti F. Neuroendocrinology. 2010;92 (Supl 1):125

---

---

---

---

---

---

---




---

---

---

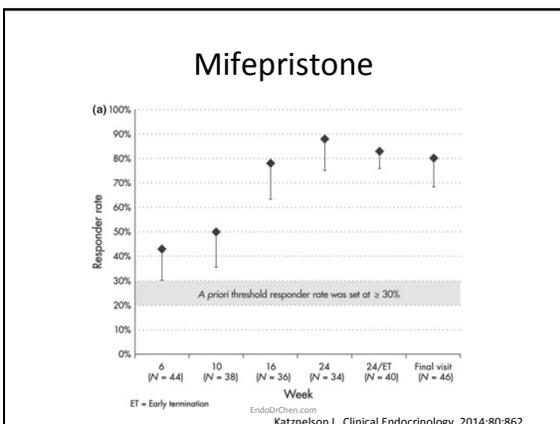
---

---

---

---

---




---

---

---

---

---

---

---

---

Statistics (mITT population)	Responder [n (%)]	Nonresponder [n (%)]	Lower bound one-sided 95% exact binomial CI (%)	P value
C-DM (n = 25) Participants with or without a ≥25% reduction from baseline in AUC <sub>glucose</sub> at wk 24/ET	15 (60)	10 (40)	41.7	<0.0001
C-HT (n = 21) Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET	8 (38.1)	13 (61.9)	20.6	<0.05
C-HT and C-DM with HTN at screening (n = 40) Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET	17 (42.5)	23 (57.5)		
Participants who had a reduction in antihypertensive medications at wk 24/ET	11 (27.5)	29 (72.5)		
Participants who had either ≥5 mm Hg reduction from baseline in DBP or had a reduction in antihypertensive medications at wk 24/ET	21 (52.5) <sup>a</sup>	19 (47.5)		
Median clinical improvement score of +1 at any reviewed visit <sup>b</sup>				
Combined cohorts (n = 46)	40 (87.0)	6 (13.0)	75.9	<0.0001
C-DM (n = 25)	23 (92.0)	2 (8.0)	76.9	
C-HT (n = 21)	17 (81.0)	4 (19.0)	61.6	

EndoOrChen.com  
Flaseriu M. J Clin Endocrinol Metab. 2012;97:2039

---

---

---

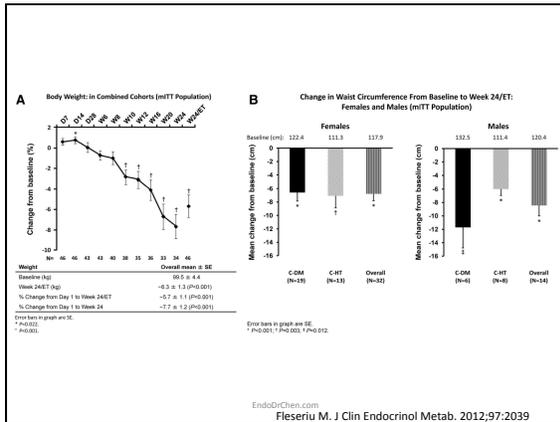
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

### Mifepristone

- Mejoría en hba1c, peso, presión arterial
- Náusea 48%, fatiga 48%, cefalea 44%, hipokalemia 34%, artralgia 30%, vómitos 26%, edema periférico 26%, hipertensión 24%, mareos 22%, hiporexia 20%, engrosamiento endometrial 20%

EndoDrChen.com  
Fleseriu M. J Clin Endocrinol Metab. 2012;97:2039

---

---

---

---

---

---

---

---

---

---

### Conclusiones

- Sigue siendo un reto diagnósticos, sobre todo los casos leves o sin cambios francos
- Métodos de tamizaje más confiables, el papel de cortisol salival nocturno
- Tratamiento quirúrgico es de elección
- Ketoconazole con limitaciones en uso por hepatotoxicidad
- Mifepristone limitado por la forma de monitorización y disponibilidad en nuestro medio

EndoDrChen.com

---

---

---

---

---

---

---

---

---

---

Preguntas...

**chenku2409@gmail.com**  
**EndoDrChen.com**

EndoDrChen.com

---

---

---

---

---

---

---