Cushing’s Syndrome
In Human

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CUSHING’S SYNDROME

• The clinical (and biochemical) features associated with chronic exposition to glucocorticoid excess
Prevalence of clinical features of Cushing’s syndrome

(prevalence of signs significantly different among patients with proven CS or without CS, in whom CS was suspected in a series of 211 patients from Nugent)

<table>
<thead>
<tr>
<th>Feature</th>
<th>'CS'</th>
<th>'W/O CS'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity</td>
<td>0.90</td>
<td>0.03</td>
</tr>
<tr>
<td>Generalized obesity</td>
<td>0.03</td>
<td>0.62</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.64</td>
<td>0.03</td>
</tr>
<tr>
<td>Weakness</td>
<td>0.65</td>
<td>0.07</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>0.53</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum K&lt;3.6 mEq/l</td>
<td>0.25</td>
<td>0.04</td>
</tr>
<tr>
<td>Plethora</td>
<td>0.82</td>
<td>0.31</td>
</tr>
<tr>
<td>WBC &gt; 11000/mm3</td>
<td>0.58</td>
<td>0.30</td>
</tr>
<tr>
<td>Acne</td>
<td>0.52</td>
<td>0.24</td>
</tr>
<tr>
<td>Striae (red, purple)</td>
<td>0.46</td>
<td>0.22</td>
</tr>
<tr>
<td>Diastolic BP &gt; 105</td>
<td>0.39</td>
<td>0.17</td>
</tr>
<tr>
<td>Edema</td>
<td>0.38</td>
<td>0.17</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>0.50</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Not different: oligomenorrhea, female, abnormal GTT.
CUSHING’S SYNDROME
- Diagnostic strategy -

THREE STEPS

- Demonstrate chronic hypercortisolism
- Establish its cause
- Locate the responsible tumor

CUSHING’S SYNDROME
- Chronic hypercortisolism -

Three approaches:
- Cortisol secretion is not normally suppressible.
- Urinary cortisol is increased
- Plasma (salivary) cortisol has lost its normal circadian variations
CUSHING’S SYNDROME
- Chronic hypercortisolism -

-Cortisol secretion is not normally suppressible.

Suppression tests
- classic low dose dex suppression test (2 mg/day x 2 days)
- 1-mg overnight dex suppression test (1 mg dex at midnight)
24h-urinary cortisol  Midnight salivary cortisol
Syndrome de Cushing  
=  
Tumeur Endocrine

CUSHING’S SYNDROME

Cushing’s Disease

Ectopic ACTH Syndrome

« Adrenal » Cushing’s Syndrome

CHRONIC HYPERCORTISOLISM
**Etiology of 809 Cushing’s syndrome’**

(Hôpital Cochin, 1992)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>n= (%)</th>
<th>sex ratio (F/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s Disease</td>
<td>548 (68 %)</td>
<td>2.8</td>
</tr>
<tr>
<td>Ectopic ACTH syndrome*</td>
<td>58 (7%)</td>
<td>1.4</td>
</tr>
<tr>
<td>Primary adrenocortical tumor</td>
<td>199 (25 %)</td>
<td>4.2</td>
</tr>
<tr>
<td>Benign adenoma</td>
<td>111 (14 %)</td>
<td>5</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
<td>88 (11 %)</td>
<td>3.6</td>
</tr>
<tr>
<td>PPNAD’/AIMAH</td>
<td>4 (0.4 %)</td>
<td>-</td>
</tr>
</tbody>
</table>

* Bronchial neuroendocrine tumor (BNT) well differentiated («carcinoid»): 30 %, undifferentiated BNT: 15 %, thymoma: 15%, pancreatic endocrine tumor: 15%, medullary cancer of the thyroid: 10%, pheochromocytoma: 5%, others 10%”

**CUSHING’S SYNDROME**

- Establish its cause -

ACTH-Dependent?

- YES (Non suppressed plasma ACTH)
  - Pituitary-Dependent
    - [HDD +]
    - [CRH +]
    - [Cathé +]
  - Non-Pituitary-Dependent
    - [HDD -]
    - [CRH -]
    - [Cathé -]

- NO (Suppressed plasma ACTH)
  - Adrenal Cushing’s syndrome
# ACTH-dependent Cushing’s syndrome

<table>
<thead>
<tr>
<th>CLINICAL</th>
<th>ANATOMICAL</th>
<th>MOLECULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical « Silent »</td>
<td>Micro adenoma</td>
<td>- ?</td>
</tr>
<tr>
<td></td>
<td>Macro adenoma (cancer)</td>
<td>- ?</td>
</tr>
<tr>
<td>Occult Aggressive</td>
<td>Carcinoid SCCL</td>
<td>- V3-R (legitimate !)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- E2F</td>
</tr>
</tbody>
</table>

**Micro adénome**
Macro adénomes

Sécrétion Ectopique d’ACTH
Carcinoides bronchiques « occultes »
Cancer anaplasique du poumon avec Sécrétion ectopique d’ACTH

« ADRENAL » CUSHING’S SYNDROME

- **Adenoma**
  - Sporadic, Isolated

- **Carcinoma**
  - Sporadic, Isolated
  - Syndromic (BWS, LF)

- **PPNAD**
  - Primary Pigmented Nodular Adrenal Disease
  - Isolated
  - Familial, Syndromic (Carney Complex)

- **AIMAH**
  - ACTH Independent-Macronodular Adrenal Hyperplasia
  - Isolated
  - Familial
  - Syndromic (McCune-Albright)
Adénome cortico surrénal

CT Scan
spontaneous density 27UH

PET Scan
18-FDG uptake

Adrenal cortical carcinoma
Carney complex

The complex of myxomas, spotty pigmentation, and endocrine overactivity.

Medicine, 1985, J Aidan Carney

PRKAR1A and 17q22-24 locus

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spotty skin pigmentation</td>
<td>77%</td>
</tr>
<tr>
<td>Skin Myxoma</td>
<td>33%</td>
</tr>
<tr>
<td>Cardiac Myxoma</td>
<td>53%</td>
</tr>
<tr>
<td>PPNAD</td>
<td>26%</td>
</tr>
<tr>
<td>Breast ductal adenoma</td>
<td>3%</td>
</tr>
<tr>
<td>LCCST</td>
<td>33% (male)</td>
</tr>
<tr>
<td>Thyroid tumor</td>
<td>5%</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>10%</td>
</tr>
<tr>
<td>Melanocytic schwannoma</td>
<td>10%</td>
</tr>
</tbody>
</table>

CA Stratakis, L Kirshner, J A Carney, JCEM, 2001 (n= 338)

Primary Pigmented Nodular Adrenocortical Disease

Germ line inactivating heterozygous mutation of PRKAR1A in 40 % of the kindreds:

Hum Mol Genet, 2000

The “CCC” (Carney-Cushing-Cochin) hypothesis:

In patients referred for Cushing’s syndrome due to PPNAD, PRKAR1A mutations might be more frequent: 15/19 index cases with CCN (78 %) & 15/23 index cases with isolated PPNAD (65 %).

Introduction

Manifestations

**Lentiginose 77 %**

Lentiginose Hyperplasie des mélanocytes

+ fréquente
période péripubertaire
péri-orificielle

**Myxome cardiaque 53 %**

Cellule souche
mesenchymateuse
pluripotente

sujet jeune
toutes les cavités
récurrent

pronostic vital
accident embolique

Matrice extracellulaire
abondante
AI-MAH
(ACTH Independent- Macronodular Adrenal Hyperplasia)

« ADRENAL » CUSHING’S SYNDROME

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<th>Sporadic, Isolated</th>
<th>MOLECULAR</th>
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<tbody>
<tr>
<td>Carcinoma</td>
<td>Sporadic, Isolated</td>
<td>β-catenine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>APC</td>
</tr>
<tr>
<td>PPNAD</td>
<td>Isolated</td>
<td>IGFII, 17p13, ...</td>
</tr>
<tr>
<td>(Primary Pigmented Nodular Adrenal Disease)</td>
<td>Syndromic (BWS, LF)</td>
<td>IGFII, p53</td>
</tr>
<tr>
<td>AIMAH</td>
<td>Isolated</td>
<td>PRKARIA</td>
</tr>
<tr>
<td>(ACTH Independent-Macronodular Adrenal Hyperplasia)</td>
<td>Familial, Syndromic (Carney Complex)</td>
<td>PDE11A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>« illegitimate Rs »</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gsa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>APC</td>
</tr>
</tbody>
</table>
The multiple alterations of the cAMP pathway in endocrine tumors

Extra-cellular ligand excess”

GαS activating mutations”
PDE 11A4” Inactivating” Mutation**

PRKAR1A inactivating mutation”

Mutation or illegitimate membrane receptor expression”

Gαs βγAMPc

CREB

CRE-Response Element (CRE)

CRE-Binding Protein: CREB”

* Horvath et al. (NIH/Cochin) Nature Genetics July 2006
ACC : distant metastases

Liver : 85/202 (42 %)  
Lung : 79/202 (39%)  
Bone : 20/202 (10 %)

Cochin Series (COMETE Network) : 202 patients, mean follow-up 3.4 ± 4.4 years (0.3 to 26 years)
18FDG Pet scan in « advanced » ACC