Functioning Adreno-cortical Tumors in Children and Adolescents

Department of Endocrine Surgery

Presenters

Dr. Ritesh Agrawal
Dr. Kul Ranjan Singh
Dr. Pallav Gupta (Pathology)

April 07, 2012
Agenda

• Introduction

• Presentation of four illustrative cases

• Review of literature

• Comment by Prof. V. Bhatia
# Functioning Adrenal Tumors

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Medulla</th>
</tr>
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<tbody>
<tr>
<td><strong>Hormone</strong></td>
<td>Cortisol</td>
<td>Androgens</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>Cushing’s syndrome</td>
<td>Virilization/Precocity</td>
</tr>
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</table>
Adrenal Surgery - SGPGI experience (1990~2012)

<table>
<thead>
<tr>
<th></th>
<th>Functional</th>
<th>Non functional</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>Cortical</td>
<td>Medullary</td>
<td></td>
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<tr>
<td>Adults</td>
<td>61</td>
<td>103</td>
<td>164</td>
</tr>
<tr>
<td></td>
<td>69</td>
<td></td>
<td>233</td>
</tr>
<tr>
<td>Pediatric</td>
<td>20</td>
<td>23</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>81</td>
<td>126</td>
<td>207</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td></td>
<td>278</td>
</tr>
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</table>
## Pediatric adrenocortical tumors

### SGPGI experience

<table>
<thead>
<tr>
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<th>Adrenocortical carcinoma (ACC)</th>
<th>Adrenocortical adenoma</th>
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</thead>
<tbody>
<tr>
<td>Mixed</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Virilization</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cushing’s</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Conn’s</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nonfunctional</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>14</strong></td>
<td><strong>8</strong></td>
</tr>
</tbody>
</table>
Functioning Adrenocortical Tumors in Children & Adolescents - Unique features

- Rare (0.2% of all pediatric neoplasms)
- Fascinating spectrum of clinical features
- Need careful biochemical evaluation
- High proportion of malignancy in infancy
- Difficult to predict biological behavior
- Difficult to predict malignancy on Histopathology
- Surgeons handling these cases should be well versed with endocrine physiology and their aberrations
- Surgery remains the mainstay of treatment
  - Offers cure in benign tumors
  - Best means of palliation in malignant cases
- Multidisciplinary approach involving Pediatricians, Pediatric Endocrinologists, Surgeons, Pathologists, Geneticists
Algorithm of hormonal evaluation in a clinically suspected case of Cushing’s syndrome

**Screening test**
- Overnight DST
  - Cortisol suppressed: No hypercortisolism
  - Cortisol not suppressed: Confirmatory test

**Confirmatory test**
- Low dose DST
  - Cortisol suppressed: No Cushing’s syndrome
  - Cortisol not suppressed: ACTH

**ACTH**
- High: Pituitary origin/Ectopic ACTH production
- Low: Adrenal origin

**High dose DST**
- Cortisol not suppressed: Ectopic ACTH production
- Cortisol suppressed: Pituitary origin

**DST** = Dexamethasone suppression test


• Bhatia V. Cushing’s syndrome. Indian J Pediatr 1997;64:177-87. (review article)

Illustrative Cases
Case 1
9 years/ boy

- c/o-
  - Progressive weight gain - 1 year

(10 kg in one year)
Examination

- Weight: 35 kg
- Height: 115.3 cm
- BP: 124/80 mm Hg
Examination
Differential Diagnosis

• Cushing’s syndrome, cause?
  – ACTH independent-
    • Adrenal adenoma/ carcinoma
  – ACTH dependent-
    • Pituitary tumor (Cushing’s disease)
    • Ectopic ACTH secreting tumor
## Hormonal profile

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Value</th>
<th>Normal range</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDDST</td>
<td>1015 nmol/L</td>
<td>&lt;50</td>
<td>Confirmation of Cushing’s syndrome</td>
</tr>
<tr>
<td>HDDST</td>
<td>859.7 nmol/L</td>
<td>&lt;50</td>
<td>Non pituitary origin</td>
</tr>
<tr>
<td>ACTH</td>
<td>21.50 pg/ml</td>
<td>4-50</td>
<td>ACTH independence</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.56 nmol/L</td>
<td>0-2.8</td>
<td>Not elevated</td>
</tr>
</tbody>
</table>

- Interpretation- ACTH independent Cushing’s syndrome due to adrenal pathology
CECT Abdomen

- Homogeneous soft tissue lesion (3.4x3.1x3.5cm) in left suprarenal region – s/o left adrenal mass
Left adrenalectomy
12-Sep-2007

• Findings-
  – Tumor in body of adrenal- 4x3.5x2 cm
  – Weight- 26 gms
  – No adhesions/ metastases/ ascites
  – Cut section- Fleshy and homogeneous
Histopathology

Mitosis
AFIP Criteria for malignancy in Pediatric ACC

• Gross-
  – Tumor weight- >400 gm
  – Tumor size- >10.5 cm
  – IVC invasion
  – Periadrenal infiltration

• Microscopic-
  – Capsular invasion
  – Vascular invasion
  – Tumor necrosis
  – >15 mitoses/ 20 hpf
  – Atypical mitotic figures

• 0- absent, 1-present
• 0-2- benign, 3- indeterminate, 4-9- malignant

Histopathology

Gross
Size- 4 cm
Weight- 26 gms
No periaxillary infiltration

Mitosis <15/20 hpf
No atypical mitosis
No necrosis
No capsular or vascular invasion
Score- 0/9
Impression- Adenoma
Post operative Course

- Uneventful
- Postoperative stress doses of steroids
- Discharged on physiological doses (advice for stress doses)
- Plan- Test for recovery of HPA axis after 3 months

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>75.7 nmol/L</td>
<td>110-540</td>
</tr>
<tr>
<td>60-min after ACTH</td>
<td>322.9 nmol/L</td>
<td>&gt;540</td>
</tr>
</tbody>
</table>

- **Interpretation**- HPA axis not recovered
- Steroids continued
Preoperative 
35 kg/ 115.3 cm

8 months postoperative 
22.7 kg/ 122 cm
Case 2
3 years/ girl

- 1 ½ months-
  - Facial, axillary and pubic hair
  - Clitoromegaly
Examination

- BP: 108/68 mm Hg
- Increased facial hair
  - Birnbaum & Rose grade 3
- No cushingoid features
Examination

- Axillary hair +
Examination

- Clitoromegaly
Clinical Diagnosis

• Virilizing syndrome, source?
  – Adrenal pathology-
    • Congenital adrenal hyperplasia
    • Adenoma
    • Carcinoma
  – Ovarian
### Hormonal profile

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</tr>
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<tbody>
<tr>
<td>17 OH-Progesterone</td>
<td>3.06 nmol/L</td>
<td>&lt;5</td>
<td>CAH ruled out</td>
</tr>
<tr>
<td>Stimulated 17 OH-Progesterone</td>
<td>15.33 nmol/L</td>
<td>&lt;35</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>23.13 nmol/L</td>
<td>Undetectable</td>
<td>Virilization</td>
</tr>
<tr>
<td>DHEAS</td>
<td>7.48 µmol/L</td>
<td>&lt;1.08</td>
<td>Adrenal source</td>
</tr>
</tbody>
</table>

- **Interpretation- Virilizing syndrome due to adrenal pathology**
CECT Abdomen

- Right adrenal mass:
  - 1.9 x 1.7 x 1.7 cm
  - Homogeneous

- Left adrenal normal
Right adrenalectomy
19-Feb-2008

- Right adrenal- 5 x 3 x 1.8 cm
  - Tumor- 2.5 x 2.8 x 1.5 cm
  - Weight- 6 gms
  - Cut section- fleshy with hemorrhagic and fatty areas
- No adhesions/ metastases/ ascites
Histopathology
Histopathology

Gross
Size - 5 cm
Weight - 6 gms
No periaudrenal infiltration

Mitosis <15/20 hpf
No atypical mitosis
No necrosis
No capsular or vascular invasion
Score - 0/9
Impression - Adenoma
Follow up

• 3½ years of follow up

• Biochemical cure
  – Serum Testosterone- <0.87 nmol/L

• No recurrence

• Facial and axillary hair, clitoromegaly static
Case 3
6 months/girl

- Referred as a case of right adrenal mass with c/o-
  - Diarrhea- 4 months
  - Weight gain- 2 months
  - Irritable with ↓ sleep- 2 months
Growth rate

Centile Sequence: from top 97th, 75th, 50th, 25th, 3rd
General Examination

- Length: 56.5 cm
- Weight: 9.5 kg
- BMI: 29.8 kg/m²
- BP: 120/44 mm Hg
- Perianal excoriation present

Buffalo hump

07-Apr-2012 Functioning Adrenocortical Tum
Examination

Moon facies
# Hormonal Profile

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<tr>
<td>LDDST</td>
<td>&gt;1380 nmol/l</td>
<td>&lt;50</td>
<td>Confirmatory of Cushing’s syndrome</td>
</tr>
<tr>
<td>ACTH</td>
<td>18.2 pg/ml</td>
<td>4-50</td>
<td>ACTH independent</td>
</tr>
<tr>
<td>DHEAS</td>
<td>6.44 µmol/L</td>
<td>0.8-8.99</td>
<td>Normal</td>
</tr>
<tr>
<td>Testosterone</td>
<td>8.7 nmol/L</td>
<td>Undetectable</td>
<td>Hyperandrogenemia</td>
</tr>
</tbody>
</table>

- Interpretation- Cushing’s syndrome with Hyperandrogenemia due to adrenal pathology (?malignant)
• Right adrenal mass -
  – Well defined, hypoechoic with cystic areas
• 37 x 30 mm
- Right adrenal mass-
  - 27 x 38 mm
  - Heterogeneous
  - Solid cystic areas
Right adrenalectomy
15-Apr-2011

- Well encapsulated right adrenal mass - 4 x 4 x 3 cm
- Weight - 25 gms
- No adhesions/ metastases/ ascites
- Cut section - fleshy, variegated appearance
Histopathology

Gross
Size - 4 cm
Weight - 25 gms
No periaxial infiltration

Mitosis <15/20 hpf
No atypical mitosis
No necrosis
No capsular or vascular invasion
Score - 0/9

Impression - Adenoma
Postoperative course

• Uneventful

• Postoperative stress doses of steroids

• Discharged on physiological doses of Steroids (advice for stress doses)
Functioning Adrenocortical Tumors in Children & Adolescents

Preoperative

3-months postoperative
3-months follow up

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>10.42 nmol/L</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Cortisol Basal</td>
<td>389 nmol/L</td>
<td>110-540</td>
</tr>
<tr>
<td>60-min after ACTH</td>
<td>715 nmol/L</td>
<td>&gt;540</td>
</tr>
</tbody>
</table>

- HPA axis recovered
- Exogenous steroids stopped
- Imaging (USG abdomen and Chest X Ray)- normal
Preoperative

1-year postoperative
Case 4
15 years/ girl

• For 1 year-
  – Weight gain
  – Generalized hair growth
  – Abdominal distension
  – Facial puffiness

• Not attained menarche
Acne

Plethora

Increased Hair growth

Moon facies
Buffalo hump
Poor breast development
Central obesity
Increased hair
FG score = 21
Tinea cruris

Clitoromegaly
## Hormonal profile

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<tbody>
<tr>
<td>LDDST</td>
<td>605.7 nmol/L</td>
<td>&lt;50</td>
<td>Confirmatory of Cushing’s syndrome</td>
</tr>
<tr>
<td>HDDST</td>
<td>596.1 nmol/L</td>
<td>&lt;50</td>
<td>Non pituitary origin</td>
</tr>
<tr>
<td>Testosterone</td>
<td>7.1 nmol/L</td>
<td>0.7-2.8</td>
<td>Virilization</td>
</tr>
<tr>
<td>DHEAS</td>
<td>29.3 μmol/L</td>
<td>0.8 – 8.99</td>
<td>Adrenal origin</td>
</tr>
</tbody>
</table>

- Interpretation- Cushing’s syndrome with Virilization (?malignant)
CECT abdomen

- Right adrenal mass:
  - 9.2 x 9.0 x 8.5 cm
  - Heterogeneous
  - Areas of necrosis

- No invasion/metastases
Right adrenalectomy
23-Feb-2007

- Right adrenal mass-
  - Well encapsulated, Size- 12 x 9 x 8 cm, Weight- 410 grams
- No adhesions/ metastases/ ascites
- Cut section- Yellow brown, nodular and gritty
Histopathology
Histopathology

Necrosis
Histopathology

Gross
Size- 12 cm
Weight- 410 gms
No periaxillary infiltration

Mitosis >15/20 hpf
Atypical mitosis +nt
Necrosis +nt
No capsular or vascular invasion
Score- 5/9

Impression- Adrenocortical carcinoma
Postoperative period

- Uneventful
- Postoperative stress doses of steroids
- Discharged on physiological doses of Prednisolone (advice for stress doses)
- Plan at discharge:
  - Adjuvant therapy (Mitotane)
  - ACTH stimulation test after 3 months to see recovery of HPA axis
Preoperative  4-months after surgery
Follow up

- Attained menarche
- ACTH-stimulation test-

<table>
<thead>
<tr>
<th>Timing</th>
<th>S. Cortisol</th>
<th>Value</th>
<th>Normal</th>
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<tbody>
<tr>
<td>4-months postoperative</td>
<td>Basal</td>
<td>74.28 nmol/L</td>
<td>110-540</td>
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<tr>
<td></td>
<td>60-min after ACTH</td>
<td>205.2 nmol/L</td>
<td>&gt;540</td>
</tr>
<tr>
<td>1-year postoperative</td>
<td>Basal</td>
<td>233.4 nmol/L</td>
<td>110-540</td>
</tr>
<tr>
<td></td>
<td>60-min after ACTH</td>
<td>352.3 nmol/L</td>
<td>&gt;540</td>
</tr>
</tbody>
</table>

- Interpretation- HPA axis not recovered, steroid supplementation continued
Comparison of hormonal levels

- **DHEAS μmol/L (0.8-8.99):**
  - Preop: 29.3
  - 1 year postop: 1.48

- **Testosterone nmol/L (0.7-2.8):**
  - Preop: 7.91
  - 1 year postop: 0.98
Recurrence

• 14 months after surgery-
  – Left hypochondrium subcutaneous nodule-
    FNAC +ve for malignant cells
  – Bilateral lung metastases

• Expired within 2 months
Review
Epidemiology

- Rare (Incidence: 1-2/ million per year)
- Usually sporadic
- May be a part of hereditary syndromes

## Presentation

<table>
<thead>
<tr>
<th>Function</th>
<th>Michalkiewicz et al, 2004</th>
<th>Sutter and Grimberg, 2006</th>
</tr>
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<tbody>
<tr>
<td><strong>Virilization</strong></td>
<td>55.1%</td>
<td>50-84%</td>
</tr>
<tr>
<td>Mixed</td>
<td>29.2%</td>
<td>...</td>
</tr>
<tr>
<td>Cushing’s</td>
<td>5.5%</td>
<td>15-40%</td>
</tr>
<tr>
<td>Feminization</td>
<td>...</td>
<td>7%</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
<td>...</td>
<td>1-4%</td>
</tr>
<tr>
<td>Non functional</td>
<td>10.2%</td>
<td>...</td>
</tr>
</tbody>
</table>
Evaluation

• Clinical-
  – History
  – Examination
• Biochemical & Hormonal
• Imaging
• Genetic profile if indicated and feasible
Staging systems

- McFarlane/ Sullivan 1978/ AJCC 2002
- UICC/ WHO (TNM) 2004
- IPACTR 2004
- ENSAT 2008
- COG 2011
**Treatment**

- **Surgery**-
  - Treatment of choice (whenever possible)

- **Adjuvant medical management (in advanced stages/ unresectable tumors)**-
  - **Mitotane (M)**-
    - Narrow therapeutic window
    - Significant CNS, GI toxicity
  
  - **Cytotoxic chemotherapy**
    - EDP (Etoposide, Doxorubicin, Cisplatin)
    - Streptozotocin (Sz)

  - **Radioresistant**
Ongoing and Future research

- Trials-
  - Berrutti, 2005- (M+EDP)
  - Khan, 2000- (M+Sz)

- Ongoing International trials-
  - FIRM-ACT- M+Sz vs. M+EDP
  - Adiuvo- adjuvant M vs. follow-up only
  - IGF I & IGF II receptor antagonists
  - mTOR antagonists
Take home message

- Rare entity
- Varied presentations
- Complex hormonal interplay
- Needs expertise in evaluation and management
- Multidisciplinary approach
- Surgery offers the only chance of cure
- Regular follow up
Acknowledgements

• Departments of-
  – Endocrinology
  – Pathology
  – Radiodiagnosis
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THANK YOU