Development of a screening tool differentiating patient symptoms in Cushing’s, polycystic ovarian and metabolic syndromes

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DISCLOSURES

• Consultation:
  – Chiasma Inc.
  – Ipsen Biopharmaceuticals.
  – Novartis Pharmaceuticals Corporation

  – Nothing with respect to this presentation
Diagnostic Dilemma

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Patient Presenting Symptoms: All patients

- Weight gain / difficulty with weight loss
- Fatigue
- Blurry vision
- Polyuria and polydipsia
- Hirsutism
- Amenorrhea / hypogonadism / Infertility
Presenting Signs:

- Hypertension
- Increased: BMI >30
- Midsection weight
- Facial rounding
- Dorsocervical hump
- Hyperglycemia: Diabetes Mellitus type 11
- Fatty liver
- Hyperlipidemias
THE CLINICAL PROBLEM:

- Differential diagnosis
- Timely vs delayed diagnosis
- Appropriate efficacious treatment
Differential Diagnoses:

- Metabolic Syndrome
- Polycystic Ovarian Disease
- Cushing’s Disease
Metabolic Syndrome: Defined

Any 3 of 5 risk factors:

<table>
<thead>
<tr>
<th>Insulin resistance</th>
<th>Fasting glucose &gt; 100mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity: Increased waist circumference</td>
<td>(≥ 30.00)</td>
</tr>
<tr>
<td></td>
<td>Male &gt; 90cm (36 inches)</td>
</tr>
<tr>
<td></td>
<td>Female &gt; 80cm (32 inches)</td>
</tr>
<tr>
<td>Dyslipidemia:</td>
<td>triglycerides &gt;150 mg/dL</td>
</tr>
<tr>
<td>High Triglycerides</td>
<td>HDL &lt;40mg/dL Males</td>
</tr>
<tr>
<td>Low HDL</td>
<td>&lt;50mg/dL Females</td>
</tr>
<tr>
<td>Hypertension</td>
<td>B/P &gt; 130/85</td>
</tr>
<tr>
<td></td>
<td>&gt;140/90</td>
</tr>
</tbody>
</table>

(Alberti et al., 2009)
Polycystic Ovarian Disease (PCOS) : Defined

• An endocrine disorder involving:
  – Infertility/ irregular menses
  – Hyperandrogenism / hirsutism
  – Insulin resistance/ Diabetes Mellitus 11
  – Weight gain
  – in women with or without polycystic ovaries on imaging

( Legro et al., 2013; Dunaif et al., 1992 ).
Cushing’s Syndrome: Defined

- Abnormal weight gain
- A fatty dorsocervical hump
- Facial rounded
- Hypertension
- type 2 diabetes
- Abdominal striae (may be pink/purple)
Differential Treatment Modalities:

• Cushing’s Syndrome:
  – Adrenalectomy (unilateral)
  – Pituitary adenectomy

• Metabolic Syndrome
  – Lifestyle changes, diet and exercises

• Polycystic Ovarian Disease (PCOS)
  – Low androgenic birth control
  – Treatment of insulin resistance
1. To identify sentinel, patient reported symptoms and/or functional limitations that have a high specificity for CS vs metabolic syndrome (MS) or PCOS.

2. To develop a valid and reliable screening tool and scoring guide for use in primary care settings indicating the need for specialty referral.
Method:

• A 205 item questionnaire
• Prospectively administered at patient presentation
• Symptoms and perceived dysfunction
• Progressive severity: 6 point Likert scale (0-5)
• Patients divided into 3 groups: CS, MS, PCOS
• Control group was solicited from community
Analysis:

• Item analysis: questions reliability
• Difference between groups: ANOVA, Tamhane’s post hoc analysis
• ROC analysis sensitivity and specificity for each diagnosis using PSAW 18.
Modified scales:

- Beck Depression Inventory
- Eysenck Personality scale
- Epworth Sleepiness Scale
- Krupp Fatigue Severity Scale
- Functional Assessment Rating Scale
- Symptoms of pituitary diseases derived from review of literature and patient interviews.
Cushing’s Syndrome Screening Tool (CSST)

205 Items
item analysis
n=127

56 Items
Cronbach’s’ Alpha = 0.97

10 Items
CS vs MS vs PCOS
p => 0.05

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<table>
<thead>
<tr>
<th>I have:</th>
<th>Not at all</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Facial flushing or redness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2 A hump on the back of my neck</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3 Larger than usual breasts (males and Females)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4 Dry/coarse skin</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5 Easy sweating /body odor</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6 Dark pink/purple stretch marks on body/abdomen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7 Increasing facial rounding</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8 Persistent Hunger</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9 Swelling in feet and ankles</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10 Fatigue that disrupts my life /work life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**TOTALS**

|               | 0 | 10 | 20 | 30 | 40 | 50 |
N = 56    Groups:

• 1: Cushing’s syndrome
• 2: metabolic syndrome (MS)
• 3: PCOS
• 4: Healthy controls solicited from community volunteers.
Inclusion Criteria:

• Biochemical/pathology confirmed diagnosis of Cushing’s syndrome/disease

• Patients with Non-functioning adenomas or no pituitary or adrenal adenoma meeting criteria for PCOS and MS

• Healthy controls: No comorbidities/tumor
Exclusion Criteria:

- Unstable co-morbidities
- New treatments within 6 months of presentation
- A significant life stressor within 12 months of presentation
- Prior pituitary or adrenal surgery
Results: n= 56    14 males / 33 females

Group 1
- CUSHINGS SYNDROME (CS)
  - (3Male/11Female) n=14

Group 2
- METABLOIC SYNDROME (MS)
  - (3Male /7Female) n=10

Group 3
- POLYCYSTIC OVARIAN DISEASE (PCOS)
  - (11 Females) n=11

Group 4
- CONTROLS
  - (8 Males/13 Females) n=21
### Results:

<table>
<thead>
<tr>
<th></th>
<th>Group 1: CS</th>
<th>Group 2: MS</th>
<th>Group 3: PCOS</th>
<th>Group 4: Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N= 56</strong></td>
<td>14</td>
<td>10</td>
<td>11</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td><strong>Mean Age</strong></td>
<td>41</td>
<td>52</td>
<td>30.6</td>
<td>40.6</td>
<td>0.004 * PCOS</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>3M/11F</td>
<td>3M/7F</td>
<td>11 F</td>
<td>8M/13</td>
<td>0.01 Females</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>37.4</td>
<td>38.3</td>
<td>31</td>
<td>26.7</td>
<td>0.000 (controls)</td>
</tr>
<tr>
<td><strong>Mean severity Scores (50)</strong></td>
<td>28.2 (5-48)</td>
<td>15.1 (5-25)</td>
<td>13.3 (7-20)</td>
<td>3.7 (0-10)</td>
<td>0.000 CS</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>4 (28.6%)</td>
<td>9 (90%)</td>
<td>0</td>
<td>0</td>
<td>p&gt;0.001 MS</td>
</tr>
<tr>
<td><strong>Insulin resistance</strong></td>
<td>12 (85.7%)</td>
<td>9 (90%)</td>
<td>4 (36.3%)</td>
<td>0</td>
<td>P&gt;0.001 MS/CS</td>
</tr>
<tr>
<td><strong>HTN</strong></td>
<td>12 (85.7%)</td>
<td>8 (80%)</td>
<td>2 (18%)</td>
<td>1</td>
<td>P&gt;0.001 MS/CS</td>
</tr>
</tbody>
</table>
Cushing’s Syndrome Screening Tool (CSST)

- 10 items Cronbach’s alpha = .95
- Sensitivity = 85.7%
- Specificity = 97% (AUC= 0.965)
Conclusion:

• In study context, tool demonstrates high item reliability, sensitivity and specificity for CS.
• Did not help to differential MS from PCOS.
• CCST needs further validation in broader population.
• May be useful for differentiating patient with Cushing’s syndrome from those with both Metabolic Syndrome and Polycystic Ovarian Disease in primary care setting.
References


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Thank you.

Questions?

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