7-YEAR-OLD MALE WITH NARCOLEPSY, PRE-DIABETES, AND PRECOCIOUS PUBERTY

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CHIEF COMPLAINT

• 7 3/12 yo M referred by his PCP for evaluation of abnormal HbA1C and weight gain
HPI

• History of OSA, narcolepsy with cataplexy and 17-month weight gain
• Weight first exceeded the 95th %ile at 4 yrs of age
• 1-1.5 yrs ago: developed a ravenous appetite and nocturnal eating
  • gained 23 lbs and grew 2 inches
• Also daytime somnolence and fatigue
HPI

- Seen by PCP: Lab work (including TSH) was normal by report
- Assessment: symptoms were secondary to lifestyle
- Saw a 2nd PCP: diagnosed with insulin resistance
  - Started low-dose Adderall and metformin 500 mg daily
- 8-9 mos ago: referred to an outside endocrinologist
HPI

- Further labs done were normal by report
- Recs: feed him less and f/u with PCP
- 5 mos ago: switched from metformin to glipizide for insulin resistance
- No weight loss and continued hyperphagia
- Estimated daily caloric intake (mainly organic diet):
  - Breakfast: 600-1400, AM snack: 250, Lunch: 700, PM snack: 250, Dinner: 400 = total 2200-3000
HPI

• 1.5 mos ago: diagnosed with moderate OSA and narcolepsy following an overnight polysomnogram and multiple sleep latency test
• Started on modafinil → mild improvement in daytime fatigue
• No significant decrease in appetite
• Slowed rate of weight gain (2 lbs in the past month)
REVIEW OF SYSTEMS

Positive:
• Weight gain
• Fatigue
• Snoring
• Left-sided ptosis
• Normal cognitive development

Negative:
• Fever
• Polydipsia
• Polyuria
• Day-/nighttime enuresis
• Heat/cold intolerance
• Signs of puberty
• Drop-off in linear growth
• Vision change
• Headaches
• Anxiety or depression
FURTHER HISTORY

- **PMH**: obesity, OSA, insulin resistance, narcolepsy
- **PSH**: None
- **Allergies**: NKDA
- **Meds**:
  - glipizide 5 mg PO daily
  - modafinil 100 mg PO daily
- **SH**: Lives at home with mom, 10 yo brother, and maternal aunt. In 2nd grade, doing well.
- **FH**:
  - Alopecia totalis: mother
  - Hashimoto’s: maternal aunt and 1st cousin
  - T2DM: MGGM, Maternal great aunt
PE

- **Vitals**: T 36.1, HR 100, BP 104/58, RR 18, Wt 48.4 kg (99.9\textsuperscript{th} %ile), Ht 131cm (92\textsuperscript{nd} %ile), BMI 28 (99.7\textsuperscript{th} %ile)
- **General**: overweight, NAD, non-dysmorphic
- **HEENT**: pink MMM, PERRL, **left-sided ptosis**
- **Neck**: **No thyromegaly or nodules**
- **CV/Resp/Chest**: RRR, CTAB, no gynecomastia, +significant lipomastia
- **GU**: **Tanner 1 PH, Tanner 2 genitalia** (testes 5 mL on right, 4.5 mL on left), normal-length phallus
- **Neuro**: alert, 2+ DTRs, no focal deficits, face symmetric
- **Skin**: warm, dry, **mild acanthosis, no striae**, 1 café-au-lait patch on left chest
- **Psych**: normal mood, affect and behavior
LABS/IMAGING

- Prolactin 11.26 ng/mL
- LH 0.6 mIU/mL
- FSH 1.2 mIU/mL
- TSH 3.30 mcU/mL
- Total T4 7.7 mcg/dL
- Free T4 1.14 ng/dL
- Total testost. 8 ng/dL
- Free testost. 2 pg/mL
- Glucose 131 mg/dL
- Insulin 10.2
- HbA1C 5.8%
- CRP 1.5 mg/L
- CMP, CBC, fasting lipids- within nL limits
- Bone age xray- c/w age
- MRI pituitary- within nL limits
CLINICAL QUESTIONS

• Relationship between narcolepsy and:
  1. Obesity
  2. Precocious puberty
  3. Diabetes
NARCOLEPSY & BMI


<table>
<thead>
<tr>
<th>Level</th>
<th>Number</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>25th Percentile</th>
<th>Median</th>
<th>75th Percentile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy</td>
<td>31</td>
<td>25.53</td>
<td>6.49</td>
<td>21.37</td>
<td>22.94</td>
<td>28.52</td>
<td>48.19</td>
</tr>
<tr>
<td>Controls</td>
<td>31</td>
<td>21.41</td>
<td>3.64</td>
<td>19.08</td>
<td>20.44</td>
<td>23.31</td>
<td>33.70</td>
</tr>
</tbody>
</table>
NARCOLEPSY & BMI

- Consequence of disease-related behavior
  - E.g. reduced physical activity, increased amounts of sleep
- Decreased resting energy expenditure
  - Increased weight gain despite reduction in caloric intake
- Hyperphagia
  - Due to reduction in number of orexin-secreting neurons
- Leptin resistance with increased leptin levels
# Prevalence of Precocious Puberty

<table>
<thead>
<tr>
<th></th>
<th>Obese + Narcolepsy (42)</th>
<th>Obese w/o Narcolepsy (52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>22/20</td>
<td>29/23</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>11.4 +/- 3.59</td>
<td>11.6 +/- 3.12</td>
</tr>
<tr>
<td>BMI</td>
<td>22.2 +/- 4.39</td>
<td>29.4 +/- 4.74</td>
</tr>
<tr>
<td>mESS</td>
<td>17 +/- 7</td>
<td>7.1 +/- 1.73</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

* mESS = modified Epworth Sleepiness Scale

## Precocious Puberty

<table>
<thead>
<tr>
<th>Patients with narcolepsy</th>
<th>Prevalence, %</th>
<th>-95% CI</th>
<th>+95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese control patients</td>
<td>1.9</td>
<td>0.4</td>
<td>10.1</td>
</tr>
</tbody>
</table>

PREVALENCE OF PRECOCIOUS PUBERTY

- Indirectly related to rapid weight gain or metabolic dysregulation (related to leptin)
- Orexin may be involved in the regulation of the HPG axis, with its deficiency possibly precipitating puberty
NARCOLEPSY & DIABETES

- inappropriate activation of orexin neurons during sleep deprivation → increase in basal glucose production and a reduction in hepatic insulin sensitivity.
- Possible genetic link between narcolepsy and DM given both have a multifactorial inheritance mode.

In patients with narcolepsy, it is theorized that there is an increased prevalence of:

- **Obesity** due to disease-related behavior, decreased metabolic rate, hyperphagia, and/or leptin resistance
- **Precocious puberty** due to rapid weight gain, metabolic dysregulation, and/or orexin deficiency
- **Diabetes** due to inappropriate activation of orexin neurons, increase in basal glucose production with reduced hepatic insulin sensitivity and/or an underlying genetic link