

THE UNIVERSITY OF
MICHIGAN

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

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MEDICINE

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 (99.9th %ile), Ht 131cm (92nd %ile), BMI 28 (99.7th %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

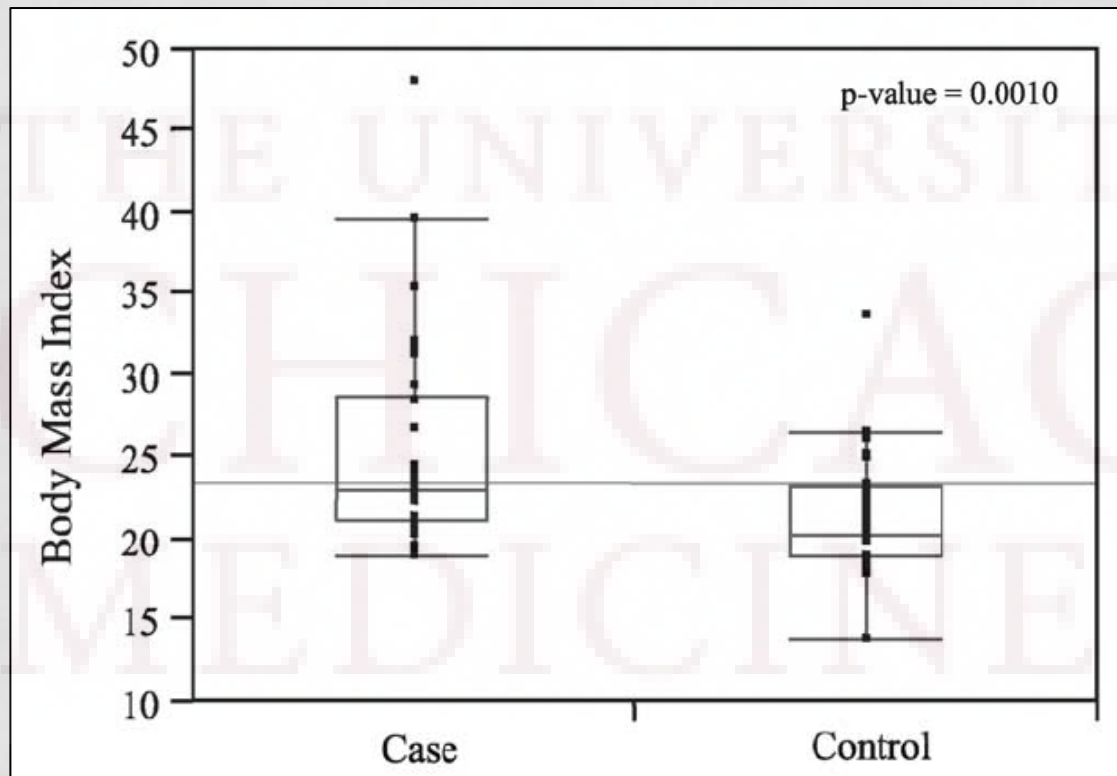
LABS/IMAGING

- 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

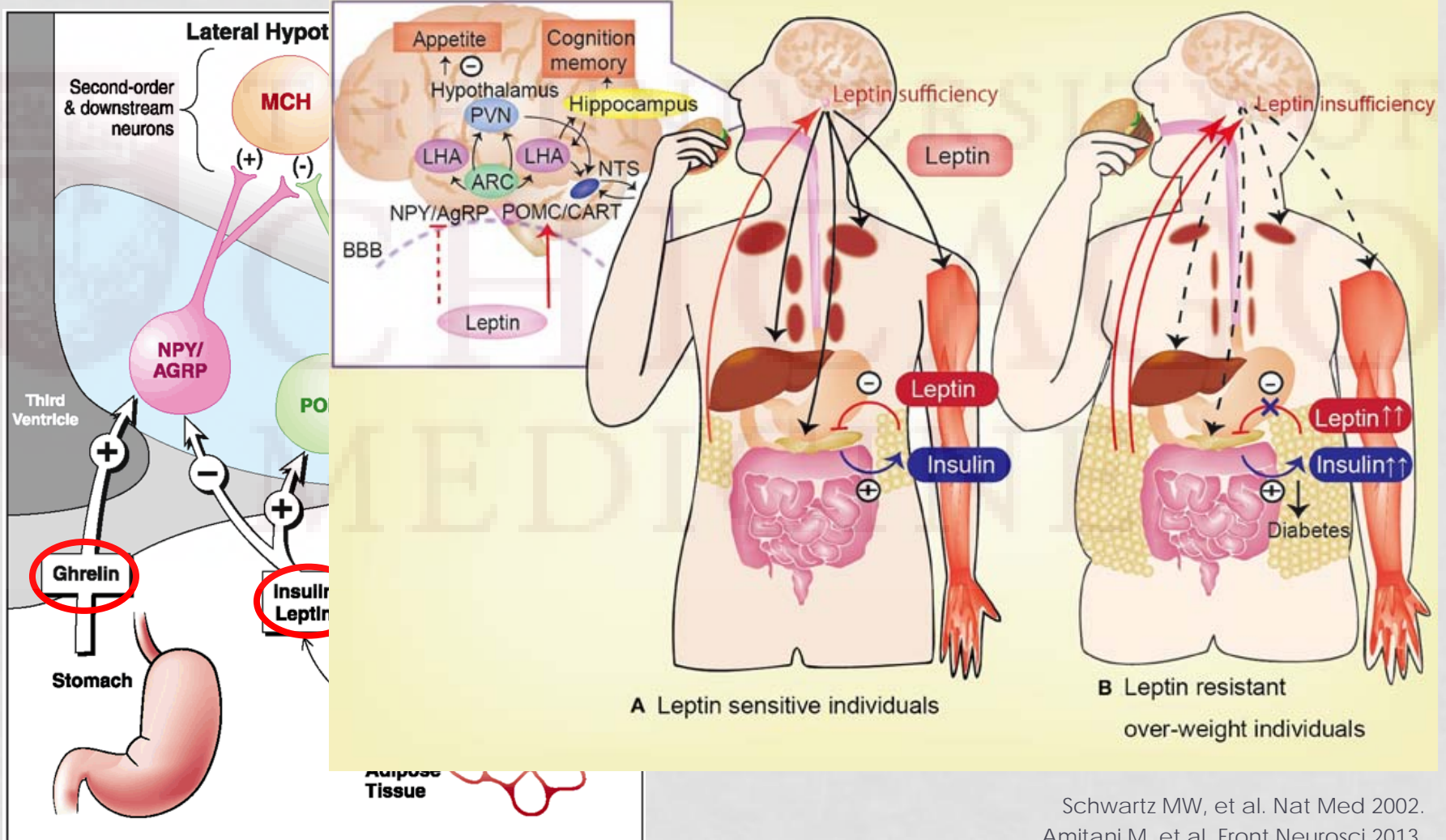


| Level | Number | Mean | Standard Deviation | 25 th Percentile | Median | 75 th Percentile | Maximum |
|------------|--------|-------|--------------------|-----------------------------|--------|-----------------------------|---------|
| Narcolepsy | 31 | 25.53 | 6.49 | 21.37 | 22.94 | 28.52 | 48.19 |
| Controls | 31 | 21.41 | 3.64 | 19.08 | 20.44 | 23.31 | 33.70 |

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

OVERVIEW



PREVALENCE OF PRECOCIOUS PUBERTY

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

- mESS = modified Epworth Sleepiness Scale

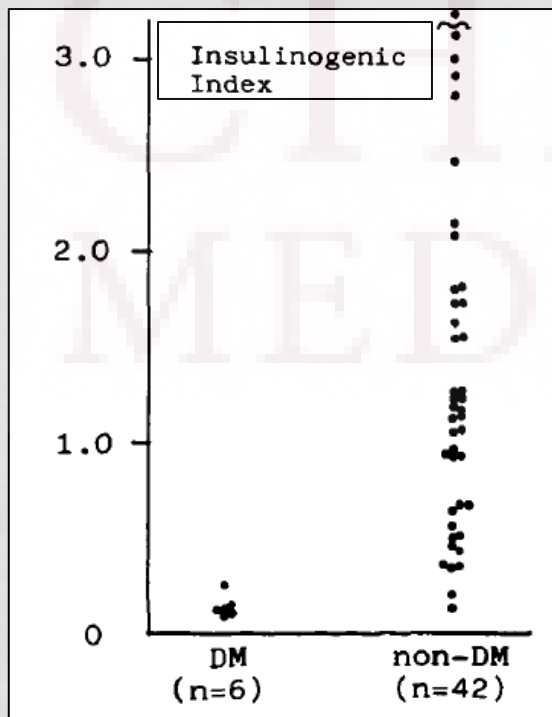
| | Precocious puberty | | |
|--------------------------|--------------------|---------|---------|
| | Prevalence, % | -95% CI | +95% CI |
| Patients with narcolepsy | 16.7 | 8.4 | 30.7 |
| Obese control patients | 1.9 | 0.4 | 10.1 |

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

| | Obese subjects (n = 24) | Nonobese subjects (n = 24) | Obesity index (mean ± SD) |
|----------------|----------------------------|-------------------------------|------------------------------|
| DM (n = 6) | 3 | 3 | 125.5 ± 24.0 |
| NonDM (n = 42) | 21 | 21 | 121.2 ± 15.3 |



- 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

SUMMARY

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

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