Monogenic and Syndromic Obesity

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Disclosures

Speaker Bureau: Rhythm Pharmaceuticals
Learning Objectives

• Review the energy balance regulation pathway.

• To introduce rare disorders of obesity, also known as monogenic obesity.

• Review clinical features of syndromic genetic disorders that cause obesity

Objectives

• To discuss the energy balance regulation

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Gut-to-brain hunger signaling

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### Monogenic Obesity

**Congenital Leptin Deficiency**

- **Cause:** mutations in gene for leptin (LEP)
- **Phenotype:** Hyperphagia with severe, early onset obesity, altered immune function and delayed puberty
- **Prevalence:** EXTREMELY RARE – only several case reports in consanguineous families*
- **Diagnostic test:** leptin level (undetectable), genetic testing
- **Treatment:** recombinant leptin


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**Leptin deficiency Case**

- Female patient with rapid early onset weight gain at 4 months of age
- Hyperphagia (demanding food continuously, ate much more than siblings)
- Developed growth abnormalities in leg bones
  - corrective leg surgery
  - liposuction of lower limb fat to try to improve mobility

Leptin deficiency
Case continued..

- Endocrine tests
  - Serum Leptin undetectable
  - Insulin (Elevated markedly)
  - Proinsulin (4 times the ULN)
- Genetic tests:
  - Homozygous LEP frameshift mutation detected
  - Parents were heterozygous
- Eligible for treatment with recombinant human leptin replacement

Leptin receptor deficiency

- **Cause:** mutations in gene for leptin receptor (LEPR)
- **Phenotype:** Hyperphagia with severe, early-onset obesity and problems with sexual development [same as leptin deficiency]
- **Prevalence:** EXTREMELY RARE - only several case reports*
- **Diagnostic test:** leptin level [very high], genetic testing
- **Treatment:** none available, MC4R agonist in development


Leptin Receptor Deficiency: What’s Next?

Leading to lack of MSH signaling

Impaired activation of POMC neurons

? Therefore, MC4R agonist might be of therapeutic benefit.
LEPR Deficiency
Case 2

• 2-year-old female presents with progressive severe obesity from birth
• Consoled only by food
• Parents were unable to maintain nutritional plan owing to hyperphagia

Case report: Leptin receptor deficiency

• No developmental delays or other abnormal clinical features present.
• Thyroid and cortisol levels normal
• Leptin levels elevated because of fat mass
• Sequenced MC4R and found no mutations
  - Subsequently sequenced 52 obesity related genes.
• Found compound heterozygous LEPR mutations
Monogenic Obesity:

- **Cause:** mutation in POMC gene
- **Phenotype:** early-onset obesity, adrenal insufficiency, red hair
- **Prevalence:** <1/1,000,000
- **Diagnostic test:** distinct phenotype, low cortisol, genetic testing
- **Treatment:**
  - Hydrocortisone replacement for adrenal insufficiency

POMC Deficiency:

Case Report

- 2-year-old Hispanic boy presents with early onset severe obesity
  - Neonatal Hypoglycemia
  - Frequent respiratory infections
  - Speech and motor delay
- Marked Hyperphagia
- Associated Adrenal Insufficiency and hypothyroidism
  - Hydrocortisone and levothyroxine replacement
POMC Deficiency: Case 3 (cont’d)

- Negative testing for Prader-Willi syndrome
- Identified homozygous POMC mutation in exon 3
- Patient was treated with metformin
- Over a 3-year metformin treatment span, BMI decreased from 34.9 kg/m² to 32.9 kg/m²

BMI = body mass index.


POMC Deficiency: What next? MC4R agonists
Monogenic Obesity:

- **PC1/3 mutations** (Pro-hormone convertase)
  - **Cause:** mutation in PCSK1 gene
  - **Phenotype:** severe obesity, low insulin, chronic diarrhea, problems with sexual development
  - **Prevalence:** VERY rare - only several case reports*
  - **Diagnostic test:** high pro-hormone levels, genetic testing
  - **Treatment:**
    - Hormone replacement

**PCSK1 Deficiency Case Report**

- 6-year-old male with severe early onset obesity
- Malabsorptive diarrhea noted at the age of 8 days
- During first year of life required specialized formulas for weight gain
- Reported to be hyperphagic with food seeking behavior at the age of 2.

*Farooqi et al. JCEM 2007;92:3369-3373
PCSK1 Deficiency
Case 4 (cont’d)

Clinical features of severe early onset obesity, abnormal Insulin/proinsulin ratio and sequencing diagnosed with prohormone convertase (PC) 1/3 deficiency

- Elevated ACTH precursor
  (549 pmol/l  Ref range:78 pmol/l)
- Low free $T_4$

$T_4$ = thyroxine.

Monogenic Obesity:

MC4R mutations

- **Cause:** mutations in MC4R receptor (autosomal dominant)
- **Phenotype:** Normal mental status;
  - Increased fat and lean mass with increased bone mineral density
  - Accelerated linear growth (tall stature)
  - Hyperinsulinemia
- **Prevalence:** General population at 1:2000
  - Prevalence in patients with obesity :0.5 to 1%
- **Diagnosis:** genetic testing
- **Treatment:** MC4R Agonist (Rhythm) in development
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Syndromic obesity

• The most frequent forms of syndromic obesity are Prader-Willi and Bardet-Biedl syndrome.

• Not a single gene mutation but multiple genes are effected-- and have more features besides just obesity

• Mechanism of obesity is less well understood
Prader-Willi Syndrome

Prader-Willi syndrome: Genetic mechanisms

- Normal
- Paternal deletion (65-75%)
- Maternal UPD (20-30%)

http://www.genetics4medics.com/prader-willi-syndrome.html
Clinical characteristics of Prader-Willi Syndrome

• Birth to 2 years:
  Hypotonia with poor suck

• 2–6 years:
  Hypotonia with poor suck
  Global developmental delays

• 6–12 years:
  History of hypotonia with poor suck
  Global developmental delay
  Excessive eating
  (hyperphagia, obsession with food)
  Central obesity


Clinical characteristics of Prader-Willi Syndrome

12 years through adulthood

Intellectual disability
Hyperphagia with central obesity
Hypothalamic hypogonadism
Typical behavior problems
  (including temper tantrums and compulsive features)

Bardet-Biedl Syndrome (BBS)

- Mutation in BBS genes
- BBS genes are involved in trafficking LEPR to the neuronal cell surface
- Also genetic defect in cilia

Clinical Characteristics

- Diagnostic criteria: 4 primary features OR 3 primary plus 2 secondary features

  - Primary Criteria:
    - Rod cone dystrophy
    - Polydactyly
    - Obesity
    - Genital anomalies
    - Renal anomalies
    - Learning difficulties

  - Secondary Criteria:
    - Speech delay
    - Developmental delay
    - Diabetes mellitus
    - Dental anomalies
    - Congenital Heart disease
    - Brachydactyly
    - Ataxia/Poor coordination
    - Anosmia/Hyposmia

Alström syndrome: ALMS1 deficiency

- Mutation in ALMS1 gene.
- ALMS1 plays role in LEPR signaling and POMC neuron survival
- <1:1,000,000 (~900 cases)

Alström syndrome: Clinical Characteristics

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>ALMS1 mutation in 1 allele and/or family history of Alström syndrome</td>
<td>Obesity Dilated cardiomyopathy with congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Vision (nystagmus, photophobia)</td>
<td>• Obesity and/or insulin resistance</td>
</tr>
<tr>
<td>3-14</td>
<td>ALMS1 mutation in 1 allele and/or family history of Alström syndrome</td>
<td>History of dilated cardiomyopathy with congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Vision (nystagmus, photophobia, decreased acuity, cone dystrophy [sometimes diagnosed as retinitis pigmentosa]² by ERG)</td>
<td>Hearing loss</td>
</tr>
<tr>
<td>&gt;15</td>
<td>ALMS1 mutation in 1 allele and/or family history of Alström syndrome</td>
<td>Advanced bone age</td>
</tr>
<tr>
<td></td>
<td>Vision (legal blindness, history of nystagmus in infancy/childhood, cone and rod dystrophy by ERG)</td>
<td>Hepatic dysfunction</td>
</tr>
</tbody>
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² by ERG
Albright Hereditary Osteodystrophy

- Inactivating mutation in GNAS
  Inherited from the mother, can be associated with resistance to certain hormones, in particular the PTH. This is Pseudohypoparathyroidism type 1A.

- When inherited from father, no hormone resistance but an AHO phenotype.

Albright Hereditary Osteodystrophy phenotype

- Developmental delay
- Short stature
- Round facies
- Short fourth and fifth metacarpals
- Brachydactyly
- Hypocalcemia (in PHP1A)
Fragile X Syndrome

- Obesity in up to 60% of cases
- 1/2,500 births X-linked
- FMR1 gene (Xq27.3)
- Intellectual disability, hyperkinetic behavior, macroorchidism, large ears, prominent jaw

Benefits of Identifying Genetic Cause

- Families relieved to know cause, feel less blame
- Anticipatory guidance and screening
- Social support groups provide community
- Management of hyperphagia as a physiologic medical condition
  - Distinct approach from traditional nutritional counseling for obesity
  - Food dosed and timed similar to prescription medications
  - In hypotonic conditions, 20% to 40% lower caloric needs due to decreased lean mass
    - Growth hormone therapy approved for PWS – increases muscle mass and tone, reduces truncal obesity, potential cognitive benefits when initiated early
- Genetic diagnosis → opportunity for targeted treatment

Precision Medicine Based on Genetics

• Leptin replacement for leptin deficiency

• Melanocortin agonist (setmelanotide) under investigation for LEPR, POMC, PCSK1, and CPE mutations

• Targeted approaches being studied for other rare and common variants of leptin pathway genes