Hypothalamic obesity

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Mitochondrial Medicine Frontier Program
Center for Mitochondrial and Epigenomic Medicine
Children’s Hospital of Philadelphia

Penn Institute for Diabetes, Obesity and Metabolism

CHOP Neuroendocrinology Family Symposium
March 16, 2019
Disclosures

- Rhythm Pharmaceuticals, Hypothalamic Obesity Advisory Board
- Rhythm Pharmaceuticals, Genetic Obesity Steering Committee
- Site PI, Levo Pharmaceuticals (Prader-Willi Syndrome)
- Reata Pharmaceuticals, Advisory Board

Off-label use of medications: some medications used for weight loss are approved for other indications, and/or some may not be approved for use in children.
Gratitude

- Children’s Hospital of Philadelphia Neuroendocrine Center Faculty & Family Advisory Committee
- Chiang family
- Meeting organizers & volunteers
- Participants, patients, & families
- Attendees!

Pediatric Pituitary Brain Tumor Workshop

Saturday
March 16, 2019
Goals

• Offer ideas to review with the usual care team
• Gather priorities for care, research, and education for the CHOP Neuroendocrine Center (literally!)

Caveats

• Much remains to be learned
• No “one size fits all” solution

Notes

• “PMID” means PubMed ID (www.pubmed.gov)
• U.S. clinical trials are at: www.clinicaltrials.gov
Hypothalamic obesity is a unique clinical challenge.

What can we offer this patient that will work?
Why does obesity occur with some hypothalamic/pituitary tumors?

- **Anatomy** determines risk.
- **Tumor types include:** craniopharyngioma, astrocytoma, medulloblastoma.
- **Other risks factors:** younger age, endocrinopathy, BMI at presentation, maternal BMI.

Muller et al., Klin Padiatr 2003 (PMID: 14677094)
Roth et al., Obesity 2015 (PMID: 25884561)
Haliloglu et al., Ped Obes 2016 (PMID: 26463004)
Isn’t all obesity hypothalamic?

Proposed definition (Lustig, JCEM 2003):

- Brain tumor affecting the hypothalamus
- [At least one endocrinopathy] = evidence of damage
- Excess rate of weight gain

Lustig et al., JCEM 2003 (PMID: 12788859)
The hypothalamus perceives energy availability, and then affects intake (+, eating and storage) and output (-, satiety and expenditure)

Lustig et al., JCEM, 2003 (PMID: 12574189); Lustig, Obesity, 2011 (PMID: 22654817)
The brain does not perceive all of the energy around (stored as fat), and so goes into “starvation mode”.

“Water, water, every where, 
Nor any drop to drink”

Samuel Taylor Coleridge
*Rime of the Ancient Mariner*
Individual variation in factors contributing to hypothalamic obesity.

Hunger (need for calories)
Eating for pleasure
Taste/smell influencing food intake
Social cues to eat
Motivation to eat healthfully
Gut & fat hormones affecting satiety
Food availability

Circadian rhythms

Balance between parasympathetic & sympathetic nervous systems
Hypothalamic & pituitary hormones: thyroid, growth, adrenal, reproductive, oxytocin, vasopressin
Pancreatic insulin affecting fat storage

Excess weight gain

Physical activity
Sedentary behavior
Mood & psychosocial function
Medications

Poverty & psychosocial stress
Familial genetic factors
Decreased energy expenditure is the most consistent feature.

**Why?**

- Increased parasympathetic and decreased sympathetic activity.
- High insulin levels
- Disordered circadian rhythms
- Decreased activity
- Decreased socialization

Harz et al., JCEM 2003 (PMID: 14602754); Muller, Eur J Endo 2011 (PMID: 21490122)
Hoffman et al., JPEM (PMID: 25503864); Bomer et al., JPEM (PMID: 28097839)
What should we do?
Important background:

• **Options**: learn (& propose!) [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

• **Equipoise**: stay neutral, balanced, and detached from the outcome (even if a lot is invested)

• **Oversight**: funding agency, FDA, IRB, DSMB, investigators & participants

• **Non-FDA approved medications in research**: require IND, including certificate of analysis, demonstration of stability, microbe & pyrogen testing
Research

Clinical trials in brain tumor related obesity ongoing include:

• NCT02664441 (PI, Christian Roth, University of Washington): “Energy balance & weight loss in craniopharyngioma-related or other hypothalamic tumors in hypothalamic obesity (ECHO)”, 10-25y, exenatide (GLP1-R agonist)

• NCT02849743 (PI, Shana McCormack, CHOP): “Intranasal oxytocin for hypothalamic obesity”, 10-35y, intranasal oxytocin

• Immune modulation for new/recurrent CP, Todd Hankinson (Colorado), Eugene Hwang (Children’s National Medical Center)
Intranasal Oxytocin (OXT): Rationale for use in Hypothalamic Obesity (HypOb)

- 9-AA peptide made in hypothalamic paraventricular and supraoptic nuclei
- Animals: OXT promotes fat loss, spares lean mass.
- Obese adults: OXT may decrease energy intake and promote weight loss.
- Abnormal OXT in HypOb is plausible, and replacement may be helpful.
- Well-tolerated, but risk for hyponatremia exists.

PMID: 25865294; PMID: 27585663; PMID: 29480934; PMID: 29220529
Carbetocin (OXT analog) decreases parent-reported hyperphagia in Prader-Willi Syndrome

Dykens et al., JCI Insight 2018 (PMID: 29925684)
What are clinicians offering?

**Natural history (U.S., n=87, 86% brain tumors):**

**Hypothalamic Obesity: 4 Years of the International Registry of Hypothalamic Obesity Disorders**

Susan R. Rose, Vincent E. Horne, Nathan Bingham, Todd Jenkins, Jennifer Black, and Thomas Inge

_Rose et al., Obesity 2018 (PMID: 30296362)_
What are clinicians offering?

<table>
<thead>
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Rose et al., Obesity 2018 (PMID: 30296362)
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Rose et al, Obesity 2018 (PMID: 30296362)
Metabolic Surgery

**Likely most efficacious:**

- At 2.6 years, median decrease in BMI 8.2 kg/m² (depends on procedure)
- Mean weight loss after 6 months 20.9 kg (n=21), gastric bypass most effective (meta-analysis)
- Many likely meet ASMBS criteria for procedure (BMI 120% of 95%ile with comorbidities or 140% of 95%ile without)

Rose et al, Obesity, 2018 (PMID: 30296362)
Bretault et al., JCEM, 2013 (PMID: 23533238)
ASMBS criteria, 2018 (PMID: 30077361)
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Rose et al, Obesity 2018 (PMID: 30296362)
Pharmacotherapy (key points)

**Modest benefits need to be balanced against risks:**

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<th>Benefits</th>
<th>Risks</th>
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<td>Stimulants</td>
<td>pediatric experience may help ADHD &amp; fatigue</td>
<td>increases in heart rate and blood pressure</td>
</tr>
<tr>
<td>Metformin</td>
<td>pediatric experience may help delay diabetes</td>
<td>GI upset</td>
</tr>
<tr>
<td>GLP1-R agonists (e.g., liragultide, exenatide)</td>
<td>research &amp; some clinical pediatric experience, including craniopharyngioma</td>
<td>nausea fatigue</td>
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<td>diazoxide (+/- Metformin)</td>
<td>targets high insulin</td>
<td>fluid retention high blood sugars</td>
</tr>
<tr>
<td>octreotide</td>
<td>targets high insulin</td>
<td>gallstones high blood sugars</td>
</tr>
<tr>
<td>orlistat</td>
<td>pediatric experience</td>
<td>fat in stool</td>
</tr>
<tr>
<td>topirimate</td>
<td>pediatric experience helps with migraine</td>
<td>acidosis cognitive effects at higher doses</td>
</tr>
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**More adult experience:** Phentermine/Topirimate, Lorcaserin, Bupropion/Naltrexone, Pramlintide, Zonisamide

**Stimulants (PMID: 12197795); Metformin/fenofibrate (PMID: 25536662); Exenatide (PMID: 27133664); Octreotide (PMID: 12718557); Diazoxide/Metformin (PMID: 21603206); Systematic review in pediatric HypOb (PMID: 28544764)**
Thyroid:

- Thyroid hormone levels in the upper part of the normal range with levothyroxine (T4).
- One study of liothyronine (T3) monotherapy in CP found no change in brown fat activity, sympathetic activity, resting energy expenditure, or BMI.
- Although evidence is limited, per ATA consideration of 3-6 month trial of T4 + T3 (with small amount of T3 several times per day) is reasonable.

Van Santen et al., JPEM 2015 (PMID: 25514327)
Pituitary Replacement

**Growth hormone:**

- GH as soon as is feasible (early initiation may have benefits for weight and neuropsychological outcomes). Be thoughtful about weight-based dosing.
- “Growth without GH” can occur.
- GH has lipolytic and anabolic effects, and lower doses may be continued into adulthood.

*Boekhoff, …, Muller. Eur J Endo 2018 (PMID: 30139824)*
Pituitary Replacement

**Glucocorticoid:**

- Use lowest effective glucocorticoid replacement, be thoughtful about timing and size-based dosing.
- Lower doses may be needed, related to potential differences in cortisol metabolism (increased 11-β-HSD1 activity).
- Dose based on symptoms, endogenous function.

Hochberg et al., Horm Metab Res 2004 (PMID: 15241725)
Diet & Exercise

These are still really important!

- Prevention of co-morbidities, other benefits, including weight maintenance
- Lustig (UCSF): low-CHO diet can be used to “jump-start” efforts in some patients
- Marci Serota, speaker, RDN, & parent!
- Ensure adequate vitamin D3
- CHOP Healthy Weight Program collaboration
Indirectized monitoring:

- Incidence and severity of fatty liver may be increased
- Disrupted circadian phase may impair sleep (Dr. Xanthopoulous)
- Excess rate of mental health problems (Dr. Hocking)

Hoffman et al, Eur J Endo, 2015 (PMID: 26088821)
Lee & Bray, Obes Res, 1993 (PMID: 16353333)
Roemmler-Zehrer et al., Clin Endo, 2015 (PMID: 24923438)
Exploring integrative health:

• Mindfulness
• Acupuncture
• Aromatherapy
• Yoga
• Others

Dr. Maria Mascarenhas

Join us for this half-day symposium for adolescents, parents and caregivers to learn about integrative approaches to pediatric pain management.

SUNDAY, APRIL 7, 2019
Noon — 5 p.m.

Ruth and Raymond Gorman Research Building on the Raynolds 3, Philadelphia Campus
2520 N Center Blvd
Ground floor conference rooms
Philadelphia, PA 19104

Regenerative pain will be available in the
Roser Center for Advanced Pediatric Care.

Today, many families are looking for a comprehensive approach to health and well-being. Integrative health care focuses on the whole child and aims to prevent and treat illness through a combination of mind-body therapies such as yoga, acupuncture, aromatherapy, and other holistic medical management. It has been proven to reduce stress, pain, and improve quality of life.

Using a variety of treatment approaches allows parents to identify which strategies are most effective in managing their children’s pain and improve their quality of life.

REGISTRATION INFORMATION

There is a non-refundable registration fee of $10 per family. Registration is required for each member of the family who will attend. There will be no children available to this event. Registration is restricted to attendees 12 years and older. Snacks will be provided.

If the registration fee causes a financial burden, please email integrativehealth@email.chop.edu.

Advocacy & Research Priorities

- **Example:** 21st Century Cures Act for rare disease research, most of this through NIH & FDA

![Recommended NIH Budget, FY 2019 graph]

- **Example:** Patient-centered Outcomes Research Institute

![The 21st Century Cures Act image]

- **Example:** ICD10 diagnostic codes
Take-Home Points

• Prevention (avoiding damage) works best.
• Combination of individualized nutrition, exercise, targeted therapies, therapy for “exogenous” obesity may help, and integrative care can help.
• Consider research opportunities and metabolic surgery.
• Partner with care, research, & advocacy teams!
Additional
Isn’t all obesity hypothalamic?

“Here [in the hypothalamus] lies the very main-spring of primitive existence – vegetative, emotional, reproductive – on which with more or less success, man has come to impose a cortex of inhibitions.”

Harvey Cushing, 1929

Photo Credit: NEJM 2006
Example: Prader-Willi Syndrome

- First described by Prader, Labhart, and Willi in 1956
- Imprinting defect on chr15q11.2 (deletion of paternal copies)
- Neonatal hypotonia and failure to thrive
- Later: obesity & hyperphagia, intellectual impairment, short stature, hypogonadotropinemic hypogonadism, small hands/feet
- Value of diagnosis

Ladwirth et al., JAMA Pediatrics 1968 (PMID: 5659301)
Example: Melanocortin-4 Receptor Pathway Defects

HYPOTHALAMUS

~3% of severe, early-onset obesity cases: heterozygous mutations in MC4R

- Reduced Food Intake

LEPTIN

AgRP

POMC

α-MSH

MC4R

Pathway:

- LEPTIN activates AgRP
- AgRP activates POMC
- POMC produces α-MSH, which activates MC4R
- MC4R signaling reduces food intake
Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist

Peter Kühnen, M.D., Karine Clément, M.D., Ph.D., Susanna Wiegand, M.D., Oliver Blankenstein, M.D., Keith Gottesdiener, M.D., Lea L. Martini, M.D., Knut Mai, M.D., Ulrike Blume-Peytavi, M.D., Annette Grüters, M.D., and Heiko Krude, M.D.
Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency

Setmelanotide produced weight loss in MC4R heterozygotes and obese controls.
Sponsored protocol: www.geneticobesity.com