How We Understand Hyperphagia in PWS

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Disclosures

- Novo Nordisk (Data Safety Monitoring Committee, speaker honorarium)
- Millendo Therapeutics (Medical Advisory Board)
- Soleno Therapeutics (consultant)
- Helsinn Healthcare S.A. (consultant)
- Evidera / Rhythm Pharmaceuticals (consultant)
- Radius Health (consultant)
- Pfizer (research grant support)
- Janssen (speaker honoraria)
- Merck (speaker honorarium)
Learning Objectives

• An understanding of the nature of hyperphagia and overeating in PWS.
• An understanding of the importance of control of the food environment in management of hyperphagia in PWS.
• An understanding of the current situation regarding potential new treatments for hyperphagia in PWS.
Hyperphagia in PWS

Obese controls vs. PWS

Hyperphagia

- upset when denied a desired food
- bargain or manipulate to get more food at meals
- forage through trash for food
- eating rotten food
- eating non-food items
- get up at night to food seek
- persistent in asking or looking for food after being told no
- spending lot of time asking or talking about food
- try to sneak or steal food
- distressed when others tried to stop them asking about food
- food-related behaviour interferes with normal daily activities e.g. self-care, recreation, school or work

Nutritional Phases

0) Reduced birth weight (15-20%)
   1a) Hypotonia with difficulty feeding (0-9 mo)  
       - may also have FTT despite adequate calories  
   1b) No difficulty feeding, growing on curve (9-25 mo)

2a) Weight ↑ without ↑ in calories (2.1-4.5 y)
2b) Weight ↑ with ↑ in calories (4.5-8 y)

3) Hyperphagic, reduced satiety (>8 y)

4) Prev. 3), but appetite is less now (adulthood)

Natural History of Obesity and Hyperphagia

BMI SDS vs. Age

Age from EDD (mo)

Age vs. Eating Code

Hyperphagia

>40 mo

Butler, Holland & Goldstone. *Dev Med Child Neurology* 2009
Obesity Management

- Early diagnosis allows early institution of low-calorie, well-balanced diet
- Appropriate psychological and behavioural counselling of patient and family
- Early, repeated discussion of inevitability of hyperphagia (even in infancy)
- Rigorous supervision & control of food environment
- Restriction of access to food & money with appreciation of legal & ethical obligations
- Regular exercise
- GH helps body composition (no effect on hyperphagia known)
- Previous licensed anorexigenic agents not successful to date
- Several trial drugs have potential
- Bariatric surgery not recommended, complications +++, poor long term data

Case Report #2

Benefits Specialist PWS Residential Home for Weight

Weight loss only once in specialist PWS residential home

Benefits Specialist PWS Residential Home for Diabetes

Improved sugar control (HbA1c) and able to stop 4 out of 5 diabetes medicines including insulin only once in specialist PWS residential home

Code:
FH - family home
SRH - specialist PWS residential home
ULN - HbA1c upper limit of normal
T2DM - type 2 diabetes mellitus

T2DM since 19yo
Weight loss and improvement in sugar control (measured by HbA1c) only once in specialist PWS residential home.

Period of poor physical activity for non-medical reasons led to weight gain and worsening of sugar control.

Weight loss and improvement in sugar control (measured by HbA1c) only once in specialist PWS residential home.

Period of poor physical activity for non-medical reasons led to weight gain and worsening of sugar control.

Code:
- FH - family home
- SRH - specialist PWS residential home
- PA - physical activity
- ULN - HbA1c upper limit of normal
- T2DM - type 2 diabetes mellitus
Phenotypes of Specific PWS Gene KO / Deletion Mice

- Abnormal circadian rhythms
- Reduced male fertility
- Reduced food intake
- Mild obesity
- Reduced motor activity
- Reduced orexin cell no.
- Growth retardation
- Leptin resistance POMC neurons

Mouse 7C

- Frat3
- Mkrn3
- Magel2
- Ndn

- Exon 1, 2 or 5-7: none
- Exons 1-3 or exon 2-Ube3a:
  - FTT
  - Growth retardation

- Snrpn
- snord116
- snord115
- Ube3a-δ5
- Ube3a
- Atp10c

- Growth retardation
- Hyperphagia
- Incr EE & dysregulated circadian genes
- Abnormal 5HT-2CR mRNA processing
- Abnormal RNA editing
- None

- Wevrick, Muscatelli, Francke, Beaudet, Brannan, Lasalle
Reduced PVN Total and Oxytocin Cell Number in PWS

Human PWS hypothalamus
38% reduction in total PVN neurons
42% reduction in PVN oxytocin neurons
Swaab et al. JCEM 80:573-579, 1995

Ndn KO mouse
29% reduction in PVN oxytocin neurons
but....not obese
Monogenic Causes of Human Obesity

- Fat
- Leptin
- Hypothalamus
- Leptin receptor
- Pro-hormone convertase-1 (PCSK1)
- Pro-opiomelanocortin (POMC)
- (α-MSH)
- MC4 receptor
- Sim-1 (PVN)
- BDNF
- TrkB (BDNF receptor)
- Oxytocin
- 2nd order neurons
- NHLH2 transcription factor
- *PWS-like phenotype
Dual Hypothalamic Circuitry

Setmelanotide
MC4R agonist

Effective in POMC deficiency and LEPR mutations
Kuhnen et al. NEJM 2016
Clement et al. Nat Med 2018
Cortical Abnormalities in PWS

- Decreased parieto-occipital grey matter: 10 / 17
- Incomplete insula cortex closure: 13 / 17
- White matter lesions: 6 / 17 (especially OFC)

17 PWS subjects 11mo – 39y


Increased brain age in adults with Prader-Willi Syndrome

Manning KE, Holland AJ. Diseases. 3:382-415, 2015

Azor AM er al. Neuroimage Clin. 21:101664, 2019
Peripheral Signals Controlling Appetite

- **Leptin**
- **Glucose**
- **Insulin**
- **↓ Pancreatic polypeptide**
- **↑ Ghrelin**
- **Vagus nerve**
- **CCK**
- **PYY**
- **Oxyntomodulin**
- **GLP-1**
- Changes proportional to caloric intake
Elevated Post-Prandial Ghrelin in PWS Adults

Breakfast (522 kCal)

* P < 0.05 obese and cranio vs. PWS and non-obese

PWS
Non-obese
Obese
Craniopharyngioma

n = 6-10

Goldstone et al. JCEM 90: 2681-2690, 2005
Acyl vs. Desacyl Ghrelin

van der Lely et al. *Endocr Rev* 2004
Elevated ratio of acylated to unacylated ghrelin in children and young adults with Prader–Willi syndrome

Kuppens RJ et al. Endocrine 2015
AZP-531, an unacylated ghrelin analog, improves food-related behavior in patients with Prader-Willi syndrome: A randomized placebo-controlled trial

A

- Q1. Upset when denied food
- Q2. Try to bargain or manipulate
- Q3. Effort required to redirect
- Q4. Forage through trash for food
- Q5. Get up at night to food seek
- Q6. Persistence after being told no more
- Q7. Time spent talking about food
- Q8. Try to steal food
- Q9. Distress when told to stop food-related talk
- Q10. Cleverness in obtaining food
- Q11. Interference with daily activities

Changes in HQ individual item scores

Improvement vs. worsening

Total  9-item Behavior  Drive  Severity

* Allias S et al. PLOS ONE 2018
Livoletide

AZP01-CLI-003
double-blind Phase 2b Trial

Failure to meet primary outcomes for hyperphagia
over 3 months Livoletide 60 or 120 µg/kg
8-65 yo, HQ-CT score ≥10/36
GLP-1 Based Therapies

Drucker DJ et al. JCI 2007
Effects of MetAP2 inhibition on hyperphagia and body weight in Prader–Willi syndrome: A randomized, double-blind, placebo-controlled trial

McCandless SE et al. Diabetes Obes Metab 2017
Drug Trials for Hyperphagia in PWS

- **Beloranib** (Zafgen), *METAP2 enzyme inhibitor*, alters fat metabolism, 10% wt loss over 6 months, reduces hyperphagia scores. FDA clinical hold as PE/DVTs
- **Livoletide AZP-531** (Alize Pharma): *desacyl ghrelin analogue*
- **Setmelanotide RM-493** (Rhythm Pharmaceuticals): *MC4R agonist*
- **Rimonabant** CB1 antagonist: psychiatric side effects
- **GLWL-01 GOAT inhibitor**: no effect
- **Carbetocin** (Ferring Pharmaceuticals): *intranasal oxytocin*
- **Diazoxide**: potassium channel activator activates POMC, inhibits NPY neurons
- **Liraglutide** (NovoNordisk): *GLP-1 agonist*

No data on newer anti-obesity drugs in PWS but most now withdrawn:

- **Locaserin**: 5-HT2C receptor agonist
- **Contrave™**: Bupropion-Naltrexone
- **Qnexa™**: Phentermine-Topiramate
DCCR Phase 2 Study in PWS

Figure 3. Mean Change From Baseline to Visit 7 in Hyperphagia

Overall (n=11)  Dose ≥ 4.2 mg/kg (n=4)  BL ≥ 13 (n=6)  Dose ≥ 4.2 mg/kg BL ≥ 13 (n=3)

Change from Baseline

p=0.0055

Figure 5. Mean Changes from Baseline to Visit 7 in Body Composition by DEXA

Body Fat

p=0.02

Lean Body Mass

p=0.0592

p=0.0197

Kimonis V et al. Univ of California Irvine 2017
Diazoxide (DCCR)

c601: double-blind Ph3

c602: open label extension
Ongoing/Potential Drug Trials for Hyperphagia in PWS

- PC1-target (Levo Therapeutics): correct underlying multiple defects
- Pitolisant (Harmony Biosciences): histamine H3-receptor antagonist
- Tesomet (Saniona): tesofensine (NA, DA, 5HT reuptake inhibitor) with metoprolol,
- Cannabidiol (Radius Healthcare): multiple mechanisms
- HM04 (Helsinn): ghrelin receptor antagonist
- ?Newer GLP-1 analogue Semaglutide

www.fpwr.org/pws-clinical-trials
Hormone Processing Defects and Obesity

Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene


Human obesity has an inherited component, but in contrast to rodent obesity, precise genetic defects have yet to be defined.1 A mutation of carboxypeptidase E (CPE), an enzyme active in the processing and sorting of prohormones, causes obesity in the fa/fa mouse.2,3 We have previously described a woman with extreme childhood obesity (Fig. 1), abnormal glucose homeostasis, hypogonadotrophic hypogonadism, hypercortisolism and elevated plasma proinsulin and pro-opiomelanocortin (POMC) concentrations but a very low insulin level, suggestive of a defective prohormone processing by the endopeptidase, prohormone convertase 1 (PC1; ref. 4). We now report this proband to be a compound heterozygote for mutations in PC1. Gly109Arg63 (GGG→AGG) (Fig. 2b). This mutation, which removes a restriction site for MluI, was absent in 85 unrelated British Caucasian subjects (Fig. 2c).

The presence of this substitution in three of the proband’s four children, all of whom were clinically unaffected, suggested the possibility of an undetected mutation in

Jackson RS et al. Nat Genet 1997

RESEARCH ARTICLE

Truncating Homozygous Mutation of Carboxypeptidase E (CPE) in a Morbidly Obese Female with Type 2 Diabetes Mellitus, Intellectual Disability and Hypogonadotrophic Hypogonadism

Suzanne I. M. Alsters7,8, Anthony P. Goldstone2,3,4,6,9, Jessica L. Buxton1,8, Anna Zekavat8, Alona Sosinsky9, Andrianos M. Yiorkas1, Susan Holder1, Robert E. Klaber3, Nicola Bridges6, Mieke M. van Haesl1,8, Carol W. le Roux1,11, Andrew J. Walley12, Robin G. Walters13, Michael Mueller6, Alexandra I. F. Blakemore1

Fig. 5 Severe early-onset obesity: The proband aged 3 years, weighing 26 kg, with her father (now deceased). This photograph is reproduced with the written informed consent of the proband.

Jackson RS et al. Nat Genet 1997

PCSK1/NHLH2 Deficiency in PWS

Burnett LC et al. JCI 2016
Bariatric Surgical Procedures

Laparoscopic Gastric Banding

Vertical Sleeve Gastrectomy

Roux-en-Y Gastric Bypass

Biliopancreatic Diversion
<table>
<thead>
<tr>
<th>Yr</th>
<th>Author</th>
<th>Surgery</th>
<th>Success Rate</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>Anderson</td>
<td>(10) Gastric Bypass (1) Gastroplasty</td>
<td></td>
<td>1 wound infection 54% wt revise 1 dumping; 1 death from wt</td>
</tr>
<tr>
<td>1983</td>
<td>Touquet</td>
<td>Jejunoileal bypass</td>
<td></td>
<td>wound infection; DVT/PE</td>
</tr>
<tr>
<td>1991</td>
<td>Laurent-Jacard</td>
<td>Biliopancreatic Diversion (BPD)</td>
<td>?Wt regain 6 y</td>
<td>Diarrhoea Vit D, B12, Folate, Fe Deficient</td>
</tr>
<tr>
<td>2000</td>
<td>Grugni</td>
<td>BPD</td>
<td>Wt loss then gain</td>
<td>Diarrhoea, anemia, osteopenia, low albumin</td>
</tr>
<tr>
<td>2001</td>
<td>Marinari</td>
<td>BPD</td>
<td>Wt loss gain 20% 2y</td>
<td>2 die unrelated cause; no nutrition info at 2y</td>
</tr>
<tr>
<td>2005</td>
<td>De Almeida</td>
<td>BPD</td>
<td>Wt loss initial follow 12-28m</td>
<td>2 pts; diarrhoea in both; anaemia, 1 Vit D def</td>
</tr>
<tr>
<td>2010</td>
<td>Marceau</td>
<td>BPD/DS</td>
<td>Wt loss w/ regain</td>
<td>all 3 ? revision w/ 1 death during revision 4 years postop</td>
</tr>
</tbody>
</table>
Weight Loss at 5 Years Post-Procedure

Laparoscopic Sleeve Gastrectomy in 108 Obese Children and Adolescents Aged 5 to 21 Years

Aayed R. Alqahtani, MD, Beladvana Antonisamy, PhD, Hussam Alamri, MBBS, Mohamed Elahmedi, MBBS, and Valerie A. Zimmerman, PhD

Laparoscopic Sleeve Gastrectomy in 108 Obese Children and Adolescents Aged 5 to 21 Years

“Currently, following up 16 PWS patients who underwent LSG. Within 4-year follow up period, PWS patients have displayed a median excess BMI loss of 60.2% compared with 61.3% in non-syndromic children and adolescents with absence of significant complications.”