EMERGING THERAPIES FOR PRADER-WILLI SYNDROME

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DISCLOSURE
I have no conflicts to disclose
I will be discussing off label use of over-the-counter supplements and clinical trials of medications currently not labeled for use in PWS

OUTLINE
• Describe the genetics and hormonal profile of Prader-Willi Syndrome
• Outline the most common physical and behavior challenges of the syndrome
• Discuss current therapies and emerging research
PRADER WILLI SYNDROME

- First described in 1956
- The 4 H’s:
  - Hypotonia
  - Hyperphagia
  - Hypomotia
  - Hypogonadism
- Incidence 1:15,000 births
- 480,000 persons worldwide

COMMON STRENGTHS AND TALENTS

- Loving and affectionate
- Loyal
- Eager to please
- Never want to disappoint – which can lead to creative lies
- Jigsaw puzzle wizards
- Incredible memory skills
GENETIC AND ENDOCRINE PROFILE

GENETICS - IMPRINTING DEFECT

• 1981 – Deleted region on paternal chromosome 15 – FISH or microarray

• 1989 – PWS could be duplication of maternal chromosome 15 – methylation test

• This led to the understanding that the paternal region is essential

• Angelman syndrome results from the opposite situation – when the maternal region is not expressed

• There are also very rare inherited imprinting defects

15Q11-Q13
GENETICS - KNOCKOUT MOUSE FINDINGS

- NDN Necdin – expressed in hypothalamus – respiratory drive, GnRH, skin scratching, epilepsy, decreased pain sensitivity
- MAGEL2 – hypothalamus – results in decreased wakefulness, growth, increased adiposity, and abnormal pubertal patterns; decreased orexin
- SNRNP – hypotonia and impaired feeding, early mortality
- SNORD116 – expressed in hypothalamus, especially appetite control center - anxiety
- NO SINGLE REGION explains the entire phenotype

PROHORMONE CONVERTASE PC1

?UNIFYING EXPLANATION OF THE SYNDROME

- 2016 – Breakthrough research
- evidence that neuroendocrine PWS-associated phenotypes may be linked to reduced expression of prohormone convertase 1 (PC1)

ENDOCRINE PROFILE

- Growth hormone deficiency
- Small volume pituitary gland on MRI
- Mixed evidence of TSH and ACTH insufficiency
- Gonadotropin deficiency
  - Male – cryptorchidism, primary testicular insufficiency and gonadotropin insufficiency
  - Female – incomplete puberty, 4 live births, 2 with Angelman syndrome
- Hypothalamic dysfunction – temperature, pain, hunger, satiety; fMRI studies show aberrant brain responses in PWS
HYPOTHALAMUS
- Orexin/hypocretin
- Ghrelin
- Leptin
- Oxytocin – neuropeptide modulates social interactions and mother-infant bonding

PHYSICAL AND BEHAVIOR CHALLENGES

OBESITY
- Anxiety
- Relentless hunger
PHYSICAL CHALLENGES

- Hypotonia
- Hunger
- Low metabolism with sensitivity to medication dosing
- Sleep and breathing
  - central apneas in infancy
  - OSA from oral architecture or obesity
  - Cataplexy
- Hormonal abnormalities
- Fatigue/sleepiness
- Scoliosis and kyphosis
- Osteoporosis
- Gut motility abnormalities

BEHAVIORAL CHALLENGES

GAS PEDAL, NO BRAKES

- Food seeking
- Anxiety
- Cognitive deficits
- Rigidity and perseveration – “adaptability deficit disorder”
- Psychosis risk
- Skin picking
- Addictions

CURRENT THERAPIES

Discuss current therapies and emerging research
Discuss unique effects of GH on the PWS population
Describe common OTC medications used in the syndrome
CURRENT THERAPIES

• Growth hormone
  • Human chorionic gonadotropin
  • Testosterone or estrogen/progesterone
  • Monitoring for thyroid and cortisol insufficiency
  • Risk of Type 2 diabetes mellitus

GROWTH HORMONE

• Unique responses in PWS even if growth hormone deficiency is not present
• Improved BMI AND fat : muscle ratio
• Increased muscle strength and tone
• Improvement in lipid profile
• Improvement in central sleep apnea with improved responsiveness to increased levels of carbon dioxide
• Increased bone mineral density
• Improved cognition – even beyond infancy

HUMAN CHORIONIC GONADOTROPIN

• hCG – produced by the placenta – analog of LH (lutotropin) – gonadotropin
• hCG injections mimic the absent prenatal gonadotropin pulses
• Growth of testes improves surgical outcomes and may prompt spontaneous descent
• Stimulation to testes results in natural production of testosterone
• Testosterone = phallic growth
SEX HORMONES
TESTOSTERONE AND ESTRADIOL

- Essential for good bone development
- Difficult to dose properly – low metabolism
- Start low, Go slow

- Testosterone patch overnight reduces the dose by 1/3
- Estradiol patches deliver very small doses

OTC SUPPLEMENTS

- Coenzyme Q10 – essential to mitochondrial action and energy
- Carnitine – energy metabolism especially in muscle
- NAC – N-acetylcycteine – for treatment of acetaminophen overdose; reduces mucus thickness in CF – may normalize glutamate neurotransmission in addictions

SUPPLEMENTS
SUPPLEMENTS

- Coenzyme Q10 – energy
- Carnitine – energy
- NAC – N-acetylcysteine – skin picking compulsion

RESEARCH
**RESEARCH - EMERGING THERAPIES**

- Oxytocin
- Orexin
- Beloranib
- Diazoxide Choline
- Modafinil; Pitolisant “Wakix”
- Cannabidiol oil
- Ghrelin analog
- Setralanotide

**OXYTOCIN**

- Facilitation of birth, lactation, maternal behavior
- Social sensitivity and attunement necessary for human sociality and rearing a human child
- Under optimal conditions oxytocin may create an emotional sense of safety and trust
- Oxytocin dynamically moderates the autonomic nervous system

**OXYTOCIN**

- Released by mother during delivery
- Oxytocin has been shown to decrease aggressive behavior in animal studies, and improve recognition of facial emotions in adolescents with autism
- Studies show increased oxytocin levels but decreased number and size of OXT neurons which may reflect loss of regulatory feedback due to decreased oxytocin receptor expression
- Hot topic – emerging research, phase three trials
- Goal is to improve repetitive behaviors, disruption, and social communication skills
OXYTOCIN – INFANT STUDY
PHASE 2 STUDY – TAUBER ET AL 2017

• Results:
  • Sucking assessment: Normal NOMAS score ≥ 10, 8 normal, 15 ≥ 10: 2 did not normalize
  • Videofluoroscopy (swallowing): normal score >11, all infants had normal
  • Behavior score/distress with feeding: normal score > 5, entire group improved, 81% normal
  • fMRI brain connectivity: increased R superior orbitofrontal network
  • Ghrelin increased from baseline
  • Dosing: no effect of different dose schedules
  • These effects persisted for three weeks
  • “More alert, less fatigable, more expressive, less social withdrawal”

• Right superior orbitofrontal network
  • Taste, food texture, olfactory and somatosensory inputs from the mouth and other parts of the body
  • Information about faces, gestures, movement
  • Motivational behavior
  • Emotional decision-making
  • Social behavior
OXYTOCIN – CHILD STUDY
MILLER
- Double blind, placebo crossover study of 24 children age 5-11 years, five day treatment, washout four days, crossover
- Safety was confirmed but no statistical significance noted between groups
  - Scores favored improvement with oxytocin but did not reach statistical significance
- Parents reported changes in anxiety in the youngest children
- Parents reported stability of improvements gained after study concluded

OXYTOCIN – CARBETOCIN
- Not available in the US
- Primary use – post partum hemorrhage
- Orphan drug status in US specifically for PWS-selective oxytocin receptor agonist
- "selective oxytocin receptor agonist" refers to a compound that has a greater agonist activity at a human oxytocin (hOT) receptor than at a human vasopressin receptor (e.g., a human V2 (hV2) receptor) and has a greater selectivity compared to oxytocin
- Phase 2 trials completed

PHERLUV
ATTRACTANT FOR MEN AND WOMEN
- ORDER NOW!!!!
- $62.05
OREXIN
DAYTIME SLEEPINESS
• Hypocretin or orexin - a hypothalamic neuropeptide
• Regulates arousal, wakefulness, appetite
• Deficiency plays a role in cataplexy
• 58% lower orexin levels in the CSF of persons with PWS – correlated with daytime sleepiness

BELORANIB
HYPERPHAGIA
• Irreversible inhibitor of methionine aminopeptidase 2 (MetAP2), an enzyme that removes N-terminal methionine residues from newly synthesized proteins
• MetAP2 inhibitors were previously used in cancer therapy and found to reduce food intake, lower body weight, and decrease adipose tissue mass
• Clinical trials in PWS
  • phase two - 17 patients – reduced body weight and hyperphagia
  • phase 3 – 107 patients – baseline BMI 40
    • 74 completed the study of 26 weeks with reduction in BMI -4.1/-5.3 dose related
  • FDA halted study – 2 deaths from pulmonary embolism; company withdraw from trial
Clinical trial continued for hypothalamic obesity

DIAZOXIDE CHOLINE
HYPERPHAGIA
• Mimics leptin and insulin sensitivity and normalizes GABA response
• Phase 2 trial
  • 13 patients - very effective in behavior change and decrease in fat (not weight)
    • Hirsutism (?), fluid retention, hyperglycemia noted
  • Clinicaltrials.gov – other hypothalamic obesity trials with this agent
Modafinil and Pitolisant
Daytime Sleepiness

- Modafinil is a central stimulant that has been used in adults with narcolepsy and has recently been studied in adolescents with PWS with hypersomnia.
- Pilot study: modafinil was well tolerated and reduced daytime sleepiness without serious side effects, such as headache, insomnia, anxiety, or nausea.
- Clinical trials planned for a new drug “Wakix” – pilolisant, which acts upon histamine H3 receptors – trials in OSA, Parkinson’s, cataplexy, narcolepsy.

Setmelanotide
Hunger/Weight Loss

- MC4 peptide – agonist
- Rhythm Pharmaceuticals – phase two trial to begin
- Other groups with phase 2 trials:
  - Pro-opiomelanocortin (POMC) Deficiency Obesity (Homozygous or Epigenetic)
  - Leptin Receptor Deficiency Obesity
  - Bardet-Biedl Syndrome
  - Alstrom Syndrome

Cannabidiol Oil
Hyperphagia Behaviors

- INSYS Therapeutics – phase 2 trial, not yet recruiting
GHRELIN
LEPTIN
• Act on the hypothalamus for energy homeostasis through a feedback loop
• Ghrelin – the Hunger Hormone – produced in the stomach muscle tissue when the stomach is empty – secretion stops when stomach muscle is stretched (full)
• Leptin – the Satiety Hormone – made in fat cells

GHRELIN ANALOG
HYPERPHAGIA
• Acylated ghrelin increases appetite
• Unacylated ghrelin decreases appetite
• Available in France – phase two trial – 47 patients

DYSPHAGIA
SILENT ASPIRATION
• Two studies with similar outcomes
• Videofluoroscopy - silent aspiration and dysphagia in infants (n=6)
• Incomplete clearance, silent aspiration, impaired coordination of swallowing
RESEARCH TREATMENTS

- Vagal nerve stimulation
- Transcranial stimulation
- Deep brain stimulation
DEATH RESEARCH

- 40 years (1973-2015; only 8% included an autopsy.
- 486 families reported a death between the ages of 2 months and 67 years
- 70% of these deaths occurred in adulthood
- 312 had a cause of death provided and 36% died "of unknown" cause
- These reports uncovered trends that were previously unknown – gastric rupture and blood clots

TRENDING DIETS

- Stoplight diet
- Modified ketogenic diet
- Soft, lower fiber diet
- Supplements, supplements, supplements
THINGS I DIDN’T KNOW

• People with PWS can have profound behavioral challenges starting in the teens
• People do not call PWIS with happy stories
• UPD has significant risk of psychosis (60%)
• UPD is more common in IVF and older parents – the ratios are changing
• There are 2 PWS organizations in the US
• For people with developmental disabilities, living at home after high school is seldom the best plan

THINGS I DID KNOW

• Growth hormone is a game changer in PWS but we don’t know how to dose it
• Parents prefer to ask other parents on Facebook for advice rather than make a phone call
• A little compassion goes a long way
• Working from home is pretty sweet
PHARMACOGENETICS

- **Pharmacogenetics** is the study of inherited genetic differences in drug metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects.
- Antidepressants, oncology meds, pain treatment
- Liver enzyme CYP2D6 – converts morphine into codeine – could cause overdose if the individual has more than one copy of this gene
- CYP 450 testing can help determine psychotropic choices in PWS