Hypothermia in PWS

• Several case reports in middle-aged PWS
  – Recurrence risk
  – No gender bias
  – Hypothermic response to ambient cold temperature challenge

• Faulty homeostatic mechanisms
  – Abnormal pain/temperature perception (known)
  – Abnormal central sensor threshold (suspected)
  – Impaired insight and judgment
  – Cognitive inflexibility limits capacity for change
Hypothermia in PWS

• Neurobiology of thermoregulation
• Causes of hypothermia
• Somatic findings secondary to hypothermia
• Morbidity associated with hypothermia
• Case presentations
• Treatment
• Prevention
Mechanisms of Heat Loss

Radiation
- 60% total heat loss
- core to surface via circulatory system
Mechanisms of Heat Loss

Radiation
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- core to surface via circulatory system

Evaporation
- 22% total heat loss
Mechanisms of Heat Loss

Radiation
- 60% total heat loss
- core to surface via circulatory system

Evaporation
- 22% total heat loss

Conduction & Convection
- 15% total heat loss
- kinetic energy transferred from body surface to environment via laminar air/water flow
Temperature Regulation: Afferent

SKIN
TRPM-8
Cold/menthol sensor

SPINAL CORD
Temperature Regulation: Afferent

SKIN
TRPM-8

DORSAL ROOT GANGLION
50% decreased temperature/pain
Temperature Regulation: Afferent

Hypothalamus
BRAIN

DORSAL ROOT GANGLION
50% decreased temperature/pain

SKIN
TRPM-8

TRPM-8
Central Temperature Regulation

Hypothalamus

Neuronal feedback

Serotonin

Neurochemical feedback

Dopamine
Norepinephrine
Prostaglandins
Temperature Regulation: Efferent

Hypothalamus

BRAIN
Cognition & behavior

SPINAL CORD
Temperature Regulation: Efferent

Hypothalamus

BRAIN
- Cognition & behavior

THYROID (Thyroxine)
- Thermogenesis

ADRENALS (Catecholamines)
- Thermogenesis
Temperature Regulation: Efferent

Hypothalamus

BRAIN
  Cognition & behavior

THYROID (Thyroxine)
  Thermogenesis

SKIN
  Vasoconstriction
  Alpha-1-adrenergic receptors

ADRENALS
  (Catecholamines)
  Thermogenesis
Temperature Regulation: Efferent

- **Hypothalamus**
  - **BRAIN**
    - Cognition & behavior
  - **THYROID** (Thyroxine)
    - Thermogenesis
  - **MUSCLE**
    - Increased tone
    - Shivering
  - **ADRENALS** (Catecholamines)
    - Thermogenesis

- **SKIN**
  - Vasoconstriction
  - Alpha-1-adrenergic receptors

- **THYROID**
  - (Thyroxine)
  - Thermogenesis

- **MUSCLE**
  - Increased tone
  - Shivering

- **ADRENALS** (Catecholamines)
  - Thermogenesis
Causes of Hypothermia

• Central nervous system dysfunction
  – Focal, structural, generalized
  – Impaired intellectual capacity and judgment

• Metabolic disorders
  – Hypothyroidism, adrenal insufficiency, diabetes mellitus

• Age
  – Very young and very old

• Toxic effects
  – Alcohol

• Iatrogenic effects
Causes of Hypothermia

• Iatrogenic causes (medications)
  – Opioids (decrease sympathetic outflow, increase vasodilatation, increased threshold for temperature regulation)
  – ‘Beta blocker’ antihypertensives (block beta adrenergic receptors and shivering response)
  – Atypical antipsychotics (antagonize central 5-HT2A receptors, increase vasodilatation by blocking alpha adrenergic receptors in skin)
    • Risperidone, Clozapine, Olanzapine, Quetiapine, Aripiprazole, Ziprasidone
  – Anesthetics (increase vasodilatation and block central mechanisms)
Somatic Effects of Hypothermia

• Altered mental status:
  – cognitive slowing, disorientation, decreased communication

• Coagulopathy (prolonged bleeding time)
  – impaired function of clotting factors
  – Impaired platelet aggregation

• Respiratory:
  – tachypnea
  – reduced alveolar concentration
Somatic Effects of Hypothermia

- Myocardial morbidity (3X increase):
  - Mild hypothermia: tachycardia
  - Moderate hypothermia: bradycardia, dysrhythmia and ischemia
  - Pulses difficult to assess due to bradycardia and vasoconstriction
  - Dysrhythmias; atrial fibrillation
  - Conduction defects (prolonged PR, QRS, and QT) leading to heart block and ventricular fibrillation.
  - EKG can show J-waves imitating ischemic events.
Somatic Effects of Hypothermia

• Impaired immune function
  – decreased blood flow due to vasoconstriction
  – decreased leucocyte mobilization

• Electrolyte abnormalities
  – acid/base fluctuations

• Renal insufficiency
  – cold diuresis
  – hypovolemia

• Decreased metabolism and clearance of medications
  – accumulation and toxicity
Case 1: Overview

- 40 year old female
- PWS-unknown genetic subtype
- BMI = 37-40
- 4 ER admissions secondary to hypothermia resulting in 2 inpatient stays and 9 related physician office visits over 2 months

*Hypothermia results in a high utilization (cost) of medical diagnostic and treatment services across all levels of care.*
Case 1: Pertinent history

• Medical history:
  – Hypertension with elevated cholesterol
  – Bilateral Pneumonia (2010)
  – S/P Cervical (C5, C6) surgery (2010-MVA)
  – S/P Posterior spinal fusion with instrumentation (1980’s-scoliosis)

• Psychiatric diagnoses
  – Anxiety/Depression

• Allergies/ Sensitivities:
  – Lamictal (rash)
  – NSAIDS (GI upset)
  – Ultram
Case 1: Medication list

Medications prior to first episode of hypothermia:

- Abilify 5 mg QHS
- Provigil 200mg QAM
- Baclofen 20mg TID
- Pravastatin Sodium 80mg QHS
- Furosemide 60mg QAM
- Lisinopril 20mg BID
- Loratadine 10mg QD
- Omega-3-fish oils 2 caps BID

- Alendronate sodium 70mg 4 tabs Q month
- Antacid 1000mg BID
- Multivitamin 1 tab QD
- Ferrous Sulfate 325mg BID
- Vitamin D ½ tab BID
- Docusate Sodium 100mg BID
- Nasacort AQ 2 sprays ea. nostril QD
Case 1: Time course

• **12/10/10**: Temp 93.3°F (34°C); after warming temp 94.1°F (34.5°C); no action recorded at this time

• **12/15/10**: MD visit- Dx: HTN, Hypothermia; Pulmonary consult for low $O_2$ sats; Med changes: Increase Lisinopril to 40mg QD

• **12/28/10**: Sent to ER for HTN, hypothermia & unusual behaviors (response delay, confusion, jerky head movements, argumentative with staff)
Case 1: Time course

- **12/29/10**: MD visit (ER follow-up) - Check for anemia, UTI; Temp 92.2°F (33.4°C) po, pulse 80, resp 16, BP 122/70; unable to obtain O₂ sats; after warming temp 97.9°F (36.6°C); Med changes: Decrease Furosemide to 20mg 1 QD, Increase Vitamin D 400u 1 BID, Bactrim DS 1 BID for 3 days; increase fluids (H2O)

- **1/3/11**: Sent to ER-admitted; Dx: Hypothermia, R/O Adrenal Insufficiency; Temp range: 91.4-93°F (33°C-33.9°C) B/P 107/43-135/82, pulse 50-90 NSR, O₂ Sat 98% on RA; Med Changes: Decrease Lisinopril to 20mg daily; d/c Furosemide; Increase Lasix to 40mg QD; Begin Levothyroxine 50mcg QD; Magnesium oxide 1 tab QD; dc’d home 1/5/11
Case 1: Time course, cont’d

- **1/10/11**: Sent to ER-Dx: Hypothermia, Anemia; Temp range: 92.3-92.8°F (33.5°C-33.8°C), pulse 47; EKG poor quality with artifact; Sinus bradycardia without ectopy
- **1/14/11**: MD visit (ER follow-up) for hypothermia; Med changes: D/C Baclofen; Begin Robaxin 750mg TID
- **1/18/11**: Sent to ER, Admitted; Dx: Hypothermia, etiology Hypothyroidism vs. Abilify; Outpatient pan-spinal MRI ordered to r/o spinal abscess (not completed as Neurosurgeon felt it was unnecessary due to absent clinical signs); Referral to hematology and endocrinology; Med changes: d/c Abilify; dc’d to home 1/20/11
Case 1: Time course, cont’d

- **1/26/11**: MD follow-up; Temp 96.3°F (35.7°C), pulse 50, resp 22, BP 124/84, O₂ sats 94% RA; No changes

- **2/10/11**: New PCP (internal Medicine); Temp 97.8°F (36.6°C), pulse 61, BP 140/80-120/70, O₂ sats 94%; No changes

- **3/8/11**: Endocrine, **Dx: Sub-clinical hypothyroidism**; No changes

- **3/15/11**: Hematology, Temp 97.8°F (36.6°C), BP 137/95; No changes
Case 2: Overview

- 47 year old female
- PWS-unknown genetic subtype
- Medical diagnoses:
  - Mild intellectual deficiency
  - Obesity
  - Sleep apnea
  - Hypothyroidism
  - Central adrenal insufficiency
- Weight 89 kg (196 lb)
Case 2: Pertinent history

• Recurrent hypothermia-first episode 2 years ago; Required admission to MICU for treatment of bradycardia, worsening mental status, cellulitis, pancytopenia, and central adrenal insufficiency; Recovered with steroids, antibiotics; Discharged to rehab, and then, to group home.

• 5 similar episodes since then, presenting with petechiae on chest and abdomen; looks puffy (edema) with increased weight; altered mental status (less interactive; slurred speech; somnolent)
Case 2: Pertinent history, cont’d

Typical clinical course:

• To ER; hypotensive and hypothermic (temp = 80’s°F; 27-32°C); bradycardia (required pacemaker x 1)
• Laboratory findings (typically):
  – Chem 8 and thyroid studies normal;
  – Transaminitis;
  – Anemia, leukopenia;
  – Thrombocytopenia with abnormal clotting
• Treatment: stress dose of steroids + antibiotics
• Discharge to rehabilitation with gradual recovery
Case 2: Pertinent history, cont’d

• Medications at time of last episode:
  – Synthroid
  – Cortef 15 mg in AM and 5 mg in PM (double with stress)
  – Lisinopril
  – Atenolol
  – Nexium
  – Fosamax
  – Calcium and vitamins
• Last episode resolved after Atenolol dc’d
Acute Warming Interventions

• Accurate measurement of core temperature
  – low reading rectal thermometer

• *Passive* warming
  – remove wet clothing (cold diuresis)
  – warm environment
  – re-dress in layers

• *Active* warming
  – forced air convection warming
  – insulation with warming blankets
Prevention

- Manage recurrence risk
  - Seasonal monitoring of core body temperature
- Environmental interventions
  - Manage ambient temperature
  - Check for drafts
  - Limit exposure to cold
- Behavioral interventions
  - Appropriate dress for weather (layers, hats, scarves, gloves)
  - Educate, reinforce compliance with appropriate behavior
Secondary Prevention

• Monitor *(LathamCenters Protocol, 2011)*
  – With seasonal changes; ambient temp < 45°F (7°C)
    • Temp/pulse/BP QD
  – If temp < 94.5°F (34.7°C) or pulse < 60
    • Temp/pulse Q6 hr
    • O2 sats Q6 hr
    • Call PCP
    • Warming interventions
  – If temp > 94.5°F (34.7°C), temp/pulse TID for
  – If temp > 96°F (35.6°C), temp/pulse BID for
Secondary Prevention

• Warming interventions
  – Warm fluids
  – Knit hat
  – Ambient temperature > 75°F (23.8 °C)
  – Additional blankets on bed at night
  – Heating blanket when supervised

_Latham Centers Nursing Protocol, 2011_
Tertiary Prevention

• Send to ER if:
  – Temperature cannot be maintained or <93°F (34 °C)
  – Changes in cognition or behavior
  – Pulse <40
  – Cyanosis
  – Petechiae

• Educate PCP/ER staff about effects of hypothermia in PWS

_Latham Centers Nursing Protocol, 2011_
Summary: Hypothermia in PWS

• Faulty homeostatic mechanisms
  – Abnormal pain/temperature perception
  – Abnormal central sensor threshold
  – Atypical hypothermic response to ambient cold temperature challenge
  – Impaired behavioral response, insight/judgment and cognitive flexibility

• Increased susceptibility in middle-age

• Increased risk with medical/psychiatric co-morbidities
  – Thyroid, central adrenal insufficiency, diabetes mellitus
  – Psychosis/mood disorder/dementia
  – Hypertension/cardiovascular problems
  – Iatrogenic effects due to medications

• Recurrence risk must be managed
Thank you!

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