Prader Willi Syndrome: Genetic Causes and Ethical Considerations

Texas Woman's University College of Nursing
BIOL 6903 Healthcare Genetics
NURS 6033 Ethical Dimensions of Nursing
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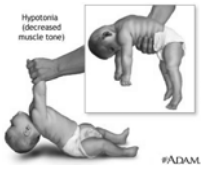
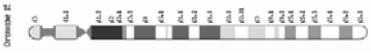
Prader Willi: Symptoms

- Infancy:
  - Difficulties establishing respirations
  - Hypotonia/Extreme hypokinesia
  - Poor suck reflex
  - Failure to thrive
  - Hypogonadism
  - Delayed milestones
  - Excessive sleeping
  - Strabismus
  - Scoliosis
  - Facies: almond shaped eyes, narrow forehead, thin upper lip, down-turned mouth

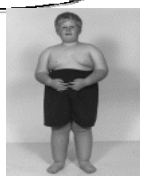


Prader-Willi Syndrome (PWS)

- Prader, Labhart, and Willi identified the cluster of symptoms and proposed that they represented a distinct syndrome in 1956.
- 1981 became known as PWS associated with an abnormality of chromosome 15 (q11-q13)



Childhood



- Learning disabilities
- Speech delay
- Poor physical coordination
- Acromicria (small hands and feet)
- Hyperphagia/failure of satiation r/t hypothalamic dysfunction
- Hypoplasia of enamel (not all persons)
- Hypopigmentaion: OCA2 gene deletion
- Excessive weight gain
- Sleep disorders

Adolescents

- Delayed onset of puberty
- Short stature: pituitary problems
- Obesity
- Extremely flexibility
- Behavioral problems: tantrums, Obsessive Compulsive Disorder, stubbornness, stealing, lying

Genetic Inheritance

- Cause: an abnormality on the proximal long arm of chromosome 15 (q11 – q13)
- Genetic imprinting
- 60 % paternal deletion
- 30-35% maternal uniparental disomy(UPD): two copies from the mother
- 5% caused by microdeletions, translocations, imprinting mutations affecting portions of the region. Results in less severe symptoms.

Adults

- Hypogonadism
- Sparse pubic hair
- Infertility
- Obesity
- Hypotonia
- Mild/Borderline/low average intelligence
- Increased risk for Type II Diabetes Mellitus
- Decreased bone mineral density

Molecular Basis

- Non-coding RNA's: small nucleolar RNA's (snoRNAs)
  - Guide chemical modification of ribosomal RNA's
  - Guide complementary base pairing
- Deletion of paternal copies of the imprinted SNRPN and NECDIN genes ;clusters of snoRNAs: SNORD64, SNORD107, SNORD108 and two copies of SNORD109, 29 copies of SNORD116 (HBII-85) and 47 copies of SNORD115 (HBII-52).
- Deletion of SNORD116 (HBII-85) has been shown to be the primary cause of Prader-Willi syndrome
- The suggested role of SNORD116 (HBII-85) is the regulation of alternative splicing.

Diagnosis

- DNA-based methylation: detects abnormal parent-specific imprinting within the Prader-Willi critical region (PWCR) on chromosome 15.
- 99% accuracy
- Important to confirm diagnosis in all patients, especially if atypical presentation.
- FISH: fluorescence in situ hybridization testing
- PCR: Polymerase Chains Reaction

Treatments

- Management of Symptoms:
  - Special nipples/gavage feedings
  - Screening for strabismus
  - OT/PT/ST
  - Hormonal therapy/surgical intervention for cryptorchidism
  - Strict supervision of daily food intake based on height, weight, BMI
  - Growth Hormone
  - Treatment of sleep disorder
  - Treatment of behavioral problems
  - Hyperphagia: no known treatment
  - Replacement of sex hormones at puberty
  - Group home

Prevalence

- 1 in 10, 00 to 1 in 30,000
  - Risk for siblings:
  - <1% if the causes is a deletion or UPD
  - 50% if the cause is a mutation of the imprinting control center
  - 25% if a parental chromosomal translocation is present

Ethical Considerations

- Autonomy: to respect a person's right to hold views, make choices and take action based on their personal values and beliefs.
- Beneficence: to act in a person's best interest
- Should we respect a person with PWS autonomy regardless of the result or protect them against the adverse consequences of their choice?

Ethical Considerations

- Autonomy
  - Does a person with PWS have the right to decide their own eating behavior and weight?
  - Is compulsory dieting ethically or legally defensible under any circumstance?
  - What is the responsibility of the family/care givers in controlling access to food and preventing potentially life threatening obesity?

Autonomy

- Decision Making Capacity:
  - Intellectual ability/disability irrelevant
  - Ability to understand, retain and believe information on healthy eating, risks of obesity relating to themselves.
  - Ability to express choice, understand one's situation, reason through consequences
  - Capacity to understand verses genetically determined behavior (control)

Autonomy

- Individual Choice:
  - Overeating behavior in PWS verses obesity
  - Knowledge of the health risk posed by obesity; we would not force treatment without consent.
  - People often stop eating before they are full to maintain weight
  - Comparable to addiction?

Autonomy

- PWS as a mental disorder
  - Mental disorder broadly defined:
    - Mental illness
    - Arrested or incomplete development of the mind
    - Psychopathic disorder or any other disorder/disability of the mind
    - 28 days without patient's consent

Autonomy

- Continued treatment without consent
  - Criteria: mental illness, psychopathic disorder, mental impairment, severe mental impairment.
  - Criteria much harder to meet
  - Significant impairment of intelligence needs to be demonstrated (IQ < 70).

Autonomy

- Drive to eat removes person's free will
- Satiety model: failure of normal feedback system triggers a drive that ensures survival
- Overeating represents free choice requiring no intervention
- Addicts can achieve abstinence; impossible to abstain from food

Autonomy

- Treating PWS as a long term mental illness is not realistic
- Would require hospitalization
- Applying these rules to life-long conditions like PWS is controversial.
- Restricting food by locking the kitchen is not "medical treatment of a mental disorder"

Beneficence

- Children with PWS
  - Parents have an ethical and legal duty to care for their child
  - Restriction of food to prevent overeating and obesity is justifiable
  - Seen as required to prevent harm; acting in the child's best interest.

Beneficence

- Adults (18 years or older)
- Best option: person with PWS consents to close supervision and food restriction
- Often not possible r/t refusal or inability to maintain plan.
- Educate, assess ability to understand and provide the least restrictive alternative

Beneficence

- Best to Experience "natural consequences"?
  - Cardio-pulmonary compromise, hyper tension, early death
  - Job losses
  - Arrests for stealing
  - Physical harm while pan-handling
  - Trading sex for food.

Beneficence

- Hyperphagia is physiological not motivational
- Food restrictions should be life long with PWS patient's
- Food restrictions in PWS patients are just as important as the life saving diets for diabetes and phenylketonuria (PKU)

Ethical Considerations

- Autonomy:
  - Hooren et.al (2002) suggested four models of autonomy involving physician-patient relationships:
  - Paternalistic
  - Informative
  - Interpretive
  - Deliberative
- Beneficence:
  - Involve patient and use least restrictive approach

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