Prader-Willi Syndrome: clinical presentations and genetic diagnosis

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Outline

Information
1. Clinical characteristics of PWS across the lifespan
2. Genetic basis of PWS
3. Diagnostic genetic testing

Objectives
1. Recognise a person who might have PWS
2. Awareness of diagnostic testing pathway
What is Prader Willi Syndrome (PWS)?

• Lifelong, multi-system condition affecting physical and mental health

• Loss of gene expression from paternal copy of chr 15q11–13

• ~ 1/10,000 to 1/30,000 liveborn incidence

• Core shared characteristics, but every person is unique

• Although there is no “cure”, physical and mental health outcomes can be greatly improved via early diagnosis and optimal management
PWS across the lifespan

Prenatal
- Decreased fetal movements
- Polyhydramnios
- Oligohydramnios
- Relatively large head to body
- Abnormal hand and foot position

Perinatal
- Increased rate of assisted delivery or C-section
- Increased rate premature and postmature births
- Birth weight typically low or low normal

Neonatal
- Hypotonia
- Poor suck
- Weak cry
- Males: undescended testes, hypoplastic scrotal sac
- Females: hypoplastic labia
Floppy babies

1. Safe neonatal care
2. Treat and test for
   1. Infection
   2. Metabolic
   3. Endocrine
3. Consider broad differential diagnosis
4. Follow local protocol for investigations
5. Watch out for dual diagnosis
6. Communicate openly and cautiously

Genetic or acquired?
Transient, stable or progressive?

Originating from:
• Central nervous system
• Spinal cord
• Neuromuscular junction
• Muscle
PWS across the lifespan

**Infancy**
- Feeding difficulties
- GORD
- Poor weight gain
- Hip dysplasia
- Strabismus
- Developmental delay

**Early childhood**
- Gradual increase in appetite and weight
- Transition to hyperphagia
- Endocrine deficiencies
- Facial and digital features
- Febrile seizures
- Developmental delay

**Later childhood**
- Obesity
- Sleep problems
- Sleep apnoea and abnormal breathing patterns
- Gastrointestinal dysmotility
- Premature adrenarche
- Learning difficulties
- Skin picking
- Repetitive and restricted behaviours
- Emotional storms
Overweight child with developmental delay

**Social and environmental**
- Diet
- Medication
- Physical exercise
- Familial

**Endocrine**
- Hypothyroidism
- Growth hormone deficiency
- Cushing syndrome

**Genetic syndromes**
- PWS
- Fragile X Syndrome
- Ciliopathies incl Bardet Biedl Syndrome
- Cohen Syndrome
- Many ultra-rare single gene disorders

IPWSO HEALTH ECHO

Lancet 2010
PWS across the lifespan

**Adolescence**
- Dietary control
- Secondary consequences of obesity
- Delayed puberty
- Scoliosis
- Intellectual disabilities
- Social interactions and relationships
- Depression and anxiety

**Early adulthood**
- Transitions to supported independence and occupation
- Management of diet and physical health
- Minimising secondary health consequences
- Low bone mineral density
- Mental health including psychosis

**Later adulthood**
- Ongoing physical and mental health needs
Genetic basis for PWS

PWS mechanisms: 3 molecular classes

- Biparental inheritance without DNA sequence mutation or epigenetic mechanism
- Imprinting centre microdeletion (10–15% patients with ID)
- Imprinting defect (ID)

IPWSO HEALTH ECHO

Smith and Hung
Translational Pediatrics 2017
Genetic basis for PWS
Genetic basis for PWS

- Deletion, 49.3%
- UPD (uniparental disomy), 35.6%
- Translocation, Schaaf–Yang, Other, 1.7%
- Don't know, 10.1%
- ID (imprinting defect), 3.3%
Genetic testing for PWS

Step 1 = paternal expression analysis (methylation specific PCR of SNRPN exon alpha) = 99% diagnostic

Step 2 = CMA (FISH) Karyotype

Step 3 = chr15 Msat markers or SNP Array Karyotype

Step 4 = Targeted deletion testing Sequencing

Step 5 = research
Summary

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THANK YOU!