Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is the most recognised form of inherited childhood obesity.

Epidemiology

- Incidence: 1 in 10 000-15 000
- All ethnic groups
- Male = Female

Genetics

- PWS results from a lack of expression of an imprinted paternal allele (SNRPN) on chromosome 15q11-13.
- Most often this is due to a deletion of the paternal allele (~60%) or maternal origin of both chromosomes 15 (uniparental disomy, ~25%) or an imprinting centre defect (~5%).
- Imprinting results in the maternally inherited SNRPN locus to be inactivated and so normal development is dependent on paternal allele expression.

Clinical Presentation

Clinical features are variable.

- Breech presentation in utero
- Feeding problems in infancy
- Failure to thrive initially
- Hyperphagia
- Truncal obesity
- Morbid obesity developing between ages 1-6 years

Physical Signs

- Almond-shaped palpebral fissures
- Down-turned corners of the mouth
- Small hands and feet.
- Hypotonia
- Microcephaly
- Hypogonadotrophic hypogonadism (males and females)
- Mental disability (IQ evenly distributed around 60 mark).
- Short stature
- Dental malocclusion (40%)
- Cryptorchidism (80%)
- Labial hypoplasia
- Micropenis
- Strabismus (40-95%)

Diagnosis

- Chromosome (FISH analysis) and DNA diagnosis demonstrating microdeletion of band 15q13-q15, uniparental disomy, or defective DNA methylation (~5%). The latter test is positive for all three categories.
- Abnormal methylation in the absence of a deletion or UPD is indicative of an imprinting centre defect.
- Methylation analysis of the SNPRN locus on chromosome 15q detects 99% of cases of PWS.

Complications

- Sexual activity is uncommon. Fertility is rare in men and uncommon in women.
- Day time sleepiness is common (50-90%)
- Respiratory problems and sleep apnoea requiring anaesthetic precautions
- Congestive heart failure due to morbid obesity
- Diabetes mellitus (15%)
- Older children and adults are often depressed

Treatment

- Emphasis is on weight management to avoid morbidity and early mortality.
- Monitoring for cognitive, behavioural and motor problems.
- Management of strabismus.
- Monitoring for sleep apnoea.
- Most adult patients with PWS require support and few will live independently. Performance in solving mazes or codes is substantially above verbal performance.
- Referral to local child development centre

Genetic Counselling:

- Deletion, uniparental disomy, or defective DNA methylation are sporadic events with a low recurrence risk for parents of affected children.
- Prenatal testing is possible at 12 weeks by CVS or later at 16-18 weeks by amniocentesis
- Affected females are at 50% risk of having a child with Angelman syndrome.

Photos
Face