

MEDICAL ALERT

A Diagnosis and Reference Guide for Physicians and Other Health Professionals

Medical Alert For Treatment Of Individuals With Prader-Willi Syndrome

Anesthesia, medication reactions

People with PWS may have unusual reactions to standard dosages of medications and anesthetic agents. Use extreme caution in giving medications that may cause sedation: prolonged and exaggerated responses have been reported. Water intoxication has occurred in relation to use of certain medications with antidiuretic effects, as well as from excess fluid intake alone.

High pain threshold

Lack of typical pain signals is common and may mask the presence of infection or injury. Someone with PWS may not complain of pain until infection is severe or may have difficulty localizing pain. Parent/caregiver reports of subtle changes in condition or behavior should be investigated for medical cause.

Respiratory concerns

Individuals with PWS may be at increased risk for respiratory difficulties. Hypotonia, weak chest muscles, and sleep apnea are among possible complicating factors. Anyone with significant snoring, regardless of age, should have a medical evaluation for obstructive sleep apnea.

Lack of vomiting

Vomiting rarely occurs in those with PWS. Emetics may be ineffective, and repeated doses may cause toxicity. This characteristic is of particular concern in light of hyperphagia and the possible ingestion of uncooked, spoiled, or otherwise unhealthful food items. The presence of vomiting may signal a life-threatening illness.

Severe gastric illness

Abdominal distention or bloating, pain and vomiting may be signs of life-threatening gastric inflammation or necrosis, more common in PWS than in the general population. Rather than localized pain, there may be a general feeling of

unwellness. If an individual with PWS has these symptoms, close observation is needed. An X-ray and an endoscopy with biopsy may be necessary to determine degree of the problem and possible need for emergency surgery.

Body temperature abnormalities

Idiopathic hyper- and hypothermia have been reported. Hyperthermia may occur during minor illness and in procedures requiring anesthesia. Fever may be absent despite serious infection.

Skin lesions and bruises

Because of a habit that is common in PWS, open sores caused by skin picking may be apparent. Individuals with PWS also tend to bruise easily. Appearance of such wounds and bruises may wrongly lead to suspicion of physical abuse.

Hyperphagia (excessive appetite)

Insatiable appetite may lead to life-threatening weight gain, which can be very rapid and occur even on a low-calorie diet. Individuals with PWS must be supervised at all times in all settings where food is accessible. Those who have normal weight have achieved this because of strict external control of their diet and food intake.

What Is Prader-Willi Syndrome?

- A disorder of chromosome 15
- Prevalence: 1 : 12,000-15,000(both sexes, all races)
- Major characteristics: hypotonia, hypogonadism, hyperphagia, cognitive impairment, difficult behaviors
- Major medical concern: morbid obesity

Cause and Diagnosis of PWS

The genetic cause is loss of yet unidentified genes normally contributed by the father. This occurs from three main genetic errors: Approximately

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70% of cases have a non-inherited deletion in the paternally contributed chromosome 15; approximately 25% have maternal uniparental disomy (UPD) - two maternal 15s and no paternal chromosome 15; and 2 - 5 % have an error in the "imprinting" process that renders the paternal contribution nonfunctional.

Major Clinical Findings

The following common characteristics of individuals with PWS raise suspicion of the diagnosis. Published diagnostic criteria include supportive findings and a scoring system (Holm et al, Pediatrics 91, 2, 1993).

- Neonatal and infantile central hypotonia, improving with age
- Feeding problems and poor weight gain in infancy
- Excessive or rapid weight gain between 1 and 6 years of age; central obesity in the absence of intervention
- Distinctive facial features - dolichocephaly in infants, narrow face/bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip and down-turned corners of mouth
- Hypogonadism - genital hypoplasia, including undescended testes and small penis in males; delayed or incomplete gonadal maturation and delayed pubertal signs after age 16, including scant or no menses in women
- Global developmental delay before age 6; mild to moderate mental retardation or learning problems in older children
- Hyperphagia/food foraging/obsession with food

Minor Findings

- Decreased fetal movement, infantile lethargy, weak cry
- Characteristic behavior problems - temper tantrums, violent outbursts, obsessive/

compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative, possessive, and stubborn; perseverating, stealing, lying

- Sleep disturbance or sleep apnea
- Short stature for genetic background by age 15
- Hypopigmentation - fair skin and hair compared with family
- Small hands and/or feet for height age
- Narrow hands with straight ulnar border
- Eye abnormalities (esotropia, myopia)
- Thick, viscous saliva with crusting at corners of the mouth
- Speech articulation defects
- Skin picking

Diagnostic testing

Individuals who have a number of the clinical findings should be referred for genetic testing. DNA methylation analysis confirms diagnosis of PWS. FISH and DNA techniques can identify the specific genetic cause and associated recurrence risk. (See ASHG/ACMG Report, Am J Hum Genet 58: 1085, 1996.) Patients who had negative or inconclusive tests with older techniques should be retested.

Recurrence risk

Significant only for rare cases with imprinting mutations, translocations, or inversions. All families should receive genetic counseling.

Weight And Behavior

Appetite Disorder

Hypothalamic dysfunction is thought to be the cause of the disordered appetite/satiety function characteristic of PWS. Compulsive eating and obsession with food usually begin before age 6. The urge to eat is physiological and overwhelming; it is difficult to control and requires constant vigilance.

Weight Management Challenge

Compounding the pressure of excessive appetite is a decreased calorie utilization in those with PWS (typically 1,000-1,200 kcal per day for adults), due to low muscle mass and inactivity. A balanced, low-calorie diet with vitamin and calcium supplementation is recommended. Regular weigh-ins and periodic diet review are needed. The best meal and snack plan is one the family or caregiver is able to apply routinely and consistently. Weight control depends on external food restriction and may require locking the kitchen and food storage areas. Daily exercise (at least 30 minutes) also is essential for weight control and health. To date, no medication or surgical intervention has been found that would eliminate the need for strict dieting and supervision around food. GH treatment, because it increases muscle mass and function, may allow a higher daily calorie level.

Behavior Issues

Infants and young children with PWS are typically happy and loving, and exhibit few behavior problems. Most older children and adults with PWS, however, do have difficulties with behavior regulation, manifested as difficulties with transitions and unanticipated changes. Onset of behavioral symptoms usually coincides with onset of hyperphagia (although not all problem behaviors are food-related), and difficulties peak in adolescence or early adulthood. Daily routines and structure, firm rules and limits, "time out," and positive rewards work best for behavior management. Psychotropic medications, particularly serotonin reuptake inhibitors such as fluoxetine and sertraline, are beneficial in treating obsessive-compulsive (OCD) symptoms, perseveration and mood swings. Depression in adults is not uncommon. Psychotic episodes occur rarely.

Developmental Concerns

Motor Skills

Motor milestones are typically delayed one to two

years; although hypotonia improves, deficits in strength, coordination, balance and motor planning may continue. Physical and occupational therapies help promote skill development and proper function. Foot orthoses may be needed. Growth hormone treatment, by increasing muscle mass, may improve motor skills. Exercise and sports activities should be encouraged and adaptations made, as needed. Proficiency with jigsaw puzzles is frequently reported, reflecting strong visual-perceptual skills.

Oral Motor and Speech

Hypotonia may create feeding problems, poor oral-motor skills and delayed speech. The need for speech therapy should be assessed in infancy. Sign language and picture communication boards can be used to reduce frustration and aid communication. Products to increase saliva may help articulation problems. Social skills training can improve pragmatic language use. Even with delays, verbal ability often becomes an area of strength for children with PWS. In rare cases, speech is severely affected.

Cognition

IQs range from 40 to 105, with an average of 70. Those with normal IQs typically have learning disabilities. Problem areas may include attention, short-term auditory memory and abstract thinking. Common strengths include long-term memory, reading ability and receptive language. Early infant stimulation should be encouraged and the need for special education services and supports assessed in preschool and beyond.

Growth

Failure to thrive in infancy may necessitate tube feeding. Infants should be closely monitored for adequate calorie intake and appropriate weight gain. Growth hormone is typically deficient, causing short stature, lack of pubertal growth spurt and a high body fat ratio, even in those with normal weight. The need for GH therapy should be assessed in both children and adults.

Sexual Development

Sex hormone levels (testosterone and estrogen) are typically low. Cryptorchidism in male infants may require surgery. Both sexes have good response to treatment for hormone deficiencies, although side effects have been reported. Early pubic hair is common, but puberty is usually late in onset and incomplete. Although it is often assumed that individuals with PWS are infertile, several pregnancies have been confirmed. Sexually active individuals should be counseled regarding the risk of pregnancy and of genetic error in offspring (50%, except for those with PWS due to UPD). Basic sex education is important in all cases to promote good health and protect against abuse.

Other Common Concerns

- **Strabismus** - esotropia is common; requires early intervention, possibly surgery
- **Scoliosis** - can occur unusually early; may be difficult to detect without X-ray; curve may progress with GH treatment. Kyphosis is also common in teens and adults
- **Osteoporosis** - can occur much earlier than usual and may cause fractures; ensure adequate calcium, vitamin D, and weight-bearing exercise; bone density test recommended
- **Diabetes mellitus, type II** - secondary to obesity; responds well to weight loss; screen obese patients regularly
- **Other obesity-related problems** - include hypoventilation, hypertension, right-sided heart failure, stasis ulcers, cellulitis and skin problems in fat folds
- **Sleep disturbances** - hypoventilation and desaturation during sleep are common, as is daytime sleepiness; sleep apnea may develop

with or without obesity; sleep studies may be needed

- **Nighttime enuresis** - common at all ages; desmopressin acetate should be used in lower than normal doses
- **Skin picking** - a common, sometimes severe habit; usually in response to an existing lesion or itch on face, arms, legs, or rectum. Best managed by ignoring behavior, treating and bandaging sores, and providing substitute activities for the hands
- **Dental problems** - may include soft tooth enamel, thick sticky saliva, poor oral hygiene, teeth grinding, and infrequently rumination. Special toothbrushes can improve hygiene. Products to increase saliva flow are helpful.

Quality of Life Issues

General health is usually good in individuals with PWS. If weight is controlled, life expectancy may be normal, and the individual's health and functioning can be maximized. The constant need for food restriction and behavior management may be stressful for family members. PWSA (USA) can provide information and support. Family counseling may also be needed. Adolescents and adults with PWS can function well in group and supported living programs, if the necessary diet control and structured environment are provided. Employment in sheltered workshops and other highly structured and supervised settings is successful for many. Residential and vocational providers must be fully informed regarding management of PWS.

Resources For Health Care Providers

"Health Care Guidelines for Individuals with PWS" and the book Management of Prader-Willi Syndrome are available from PWSA (USA), as are other publications for professionals and parents.