MEDICAL OVERVIEW

A Diagnosis and Reference Guide for Physicians and Other Health Professionals

For Treatment Of Individuals With Prader-Willi Syndrome

Life Threatening Medical Concerns

Anesthesia, medication reactions

Unusual reactions to standard dosages of medications and anesthetic agents may occur because of metabolic differences and obesity seen in PWS. A narrow airway may be present. Use extreme caution in giving medications that may cause sedation; prolonged and exaggerated responses have been reported. Several genes for GABA receptor subunits are located in the PWS chromosome region and are missing in patients with the deletion. This decrease in GABA receptors in PWS could alter the response to GABA receptor agonist sedative agents (propofol, benzodiazepines).

High pain threshold

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

Respiratory concerns

Risk may be increased for respiratory difficulties. Obesity, hypotonia, weak chest muscles, and sleep apnea are among possible complicating factors. Sleep studies for central and/or obstructive sleep apnea and hypoventilation should be obtained.

Lack of vomiting

Vomiting rarely occurs. 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. A CAT scan of the abdomen and/or endoscopy 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.

Central Adrenal Insufficiency

Studies suggest an increased incidence of CAI in individuals with PWS. Measurement of cortisol levels during a significant illness and supplementation of cortisol may be indicated.

Skin lesions and bruises

Skin picking is common in PWS, causing open sores. In some situations skin and rectal picking can be severe. 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. Water intoxication has occurred in relation to use of certain medications with anti-diuretic effects, as well as from excess fluid intake alone.

Obesity-related problems — include hypoventilation, hypertension, right-sided heart failure, stasis ulcers, cellulites and skin problems in fat folds.

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

PWS occurs from three main genetic errors. Approximately 70% of cases have a non-inherited deletion in the paternally contributed chromosome 15. Approximately 25% have maternal uniparental disomy (UPD) - two maternal 15 chromosome and no paternal chromosome 15. And 2-5 % have an error in the "imprinting" process that renders the paternal contribution nonfunctional; rarely, these imprinting defects may be inherited.

Potential Characteristics

Any infant with hypotonia should be tested for PWS. The following common characteristics raise suspicion of a diagnosis of PWS.

- Decreased **fetal movement**, infantile lethargy, weak cry
- **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 cognitive disabilities or learning problems in older children.
- **Hyperphagia**/food foraging/obsession with food
- Possible **behavior problems** — temper tantrums, obsessive/ compulsive behavior; oppositional, rigid, possessive, perseverating, can be sweet and loving
- **Sleep disturbances** especially daytime sleepiness and sleep apnea
- **Short stature** for genetic background by age 15 if untreated with growth hormone
- **Hypopigmentation** — fair skin and hair compared with family, primarily in deletion subtypes
- Small narrow **hands** and/or **feet** for height/ age. Straight ulnar border.
- **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
- **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.

- **Speech** articulation defects and dyspraxia
- **Strabismus** — esotropia is common; requires early intervention, possible surgery
- **Scoliosis** — can occur unusually early; may be difficult to detect without X-ray, kyphosis is also common in teens and adults

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. Patients who had negative or inconclusive tests with older techniques should be retested.

Recurrence risk

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

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. Adolescents and adults with PWS can function well in group and supported living programs, if the necessary diet control and structured environment are provided.

To date, no medication or surgical intervention has been found that would eliminate the need for strict dieting and supervision around food. Bariatric procedures do not address the central lack of satiety and put the individual at risk for complications.

Studies show improvement in linear growth, fat mass, motor strength, respiratory drive, and bone density with the use of **growth hormone** in PWS. Due to several deaths associated with growth hormone, precautions need to be taken prior to starting treatment including polysomnography, checking adrenal gland function and following IGF1 levels.

Resources for Health Care Providers

Please contact PWSA (USA) at 800-926-4797 with questions or to find out about additional medical resources.

IN THE EVENT OF DEATH

Reporting of Deaths

The Prader-Willi Syndrome Association (USA) has created a research database of reported deaths of individuals with PWS. In the event of death of someone with PWS, please contact PWSA (USA): 1-800-926-4797.

Organ Donation for Research

When a child or adult with PWS dies, the family may wish to consider donation of organs for research. Prompt action is essential for tissue preservation. Families are advised to contact the Brain and Tissue Bank directly: 1-800-847-1539 (Maryland)