PRADER-WILLI SYNDROME

Pws

A genetic disorder due to loss of function of specific genes on chromosome 15.

Diagnosis  Male & Female

Related Diagnoses:
Non-obstructive azoospermia

About Prader-Willi syndrome

Prader–Willi syndrome (PWS) is a genetic disorder due to loss of function of specific genes on chromosome 15. It occurs in males and females, no matter what race. As an infant, PWS shows itself in weak muscle tone (hypotonia), feeding difficulties, poor growth, and delayed development. In the beginning during childhood, characterizes itself by having the kids develop an insatiable appetite, which leads to constant overeating (hyperphagia) and obesity (Pic. 2). Some people with Prader-Willi syndrome, especially those with obesity, also get type two diabetes.

Prader-Willi syndrome is caused by the loss of genes in a specific region of chromosome 15. People normally inherit one copy of this chromosome from each parent. Some genes are active only on the copy that is inherited from a person's father. This parent-specific gene activation is caused by a phenomenon called genomic imprinting (factor that influence how some genetic conditions are inherited).

Prader-Willi syndrome occurs because certain paternal genes that should be expressed aren't for one of the following reasons:

- Paternal genes on chromosome 15 are missing.
- The person has inherited two copies of chromosome 15 from the mother and no chromosome 15 from the father.
- There's some error in the paternal genes on chromosome 15.

Angelman and Prader-Willi syndrome have both a defect in chromosome 15. If the abnormal chromosome comes from the father (paternal) you get Prader-Willi syndrome. But if the abnormal chromosome comes from the mother (maternal) baby get Angelman (a neurodevelopmental disorder characterized by severe intellectual and developmental disability).

The mainstay of diagnosis is genetic testing, specifically DNA-based methylation testing to detect the absence of the paternally contributed Prader–Willi syndrome/Angelman syndrome (PWS/AS) region on chromosome 15q11-q13. Such testing detects over 97% of cases. Methylation-specific testing is important to confirm the diagnosis of PWS in all individuals, but especially those who are too young to manifest sufficient features to make the diagnosis on clinical grounds or in those individuals who have atypical findings.

Prader–Willi syndrome has no cure; however, several treatments are in place to lessen the condition's symptoms. During infancy, subjects should undergo therapies to improve muscle strength. Speech and occupational therapy are also indicated. During the school years, children benefit from a highly structured learning environment as well as extra help. The largest problem associated with the syndrome is severe obesity. Access to food must be strictly supervised and limited.

Associated disease

- hyperphagia - abnormally increased appetite
Complications

Orthopedic Problems

Scoliosis (Pic.3) is a frequent feature observed in children with PWS (30%–70%) and may be explained partly by hypotonia and obesity. Regular clinical assessment is required at each visit, and periodic spinal X-rays are useful, whether or not the patient is receiving growth hormone (GH).

Ophthalmological Problems

Early screening and correction for myopia (a condition of the eye where light focuses in front, instead of on the retina), hypermetropia (a condition of the eye in which parallel rays are focused behind the retina), or other eye problems are recommended. Strabismus is also frequent and may require surgery.

Orthodontic Problems

Abnormal enamel and frequent caries have been previously reported, but in a recent survey PWS patients presented with a more favorable oral health status than those in previous studies. This status is worsened by poor salivary production, which requires education for both parents and children. Education for regular daily drinking and products designed to increase saliva flow might help prevent dental complications. Orthodontic treatment is often needed.

Psychological/Psychiatric Support

A characteristic behavioral profile with temper tantrums, stubbornness, controlling and manipulative behavior, compulsivity, and difficulty with change in routine becomes evident in early childhood in 70–90% of individuals with PWS. Behavioral and psychiatric problems most interfere with the quality of life in adolescence and adulthood.

Interventions concerning behavioral problems must be coordinated by specialists (psychologists, psychiatrists, and doctors), primary care providers, parents, and other family members.

Psychological support during infancy is fundamental for parents and children alike. Early logopedic therapy should be carried out to prevent language disorders. Due to their low cognitive level, PW children should receive learning support during school time.

In adolescence and adulthood some patients develop psychosis that requires pharmacological treatment.

Risk factors

- genetic predisposition

Impact on fertility

At some stage almost all subjects will require sex hormone replacement therapy. Mental retardation should not be a contraindication to allow normal pubertal development or preclude sex hormone replacement at any age in those affected individuals.

In females with PWS, the pubertal onset is very often incomplete and progressed very slowly. Women suffer from primary amenorrhea (no menstrual period) or oligomenorrhea (less frequent menstrual period). Chronic amenorrhea causes infertility, but with oligomenorrhea or temporary amenorrhea, there is still possibility to conceive a child. The use of gonadal hormone replacement should be considered if there is amenorrhea/oligomenorrhea or decreased bone mineral density (BMD). Sexual counseling and contraceptive treatment should be used as appropriate, especially in the presence of complete sexual maturation, including regular menses. There are a few case reports of pregnancy in females with PWS.
93% of men with Prader-Willi syndrome have undescended testes. At least one contributing mechanism for reduced spermatogenesis (the process in which sperms are produced from male germ cells) in cryptorchid testes (undescended testes) is temperature. The temperature of testes in the scrotum is at least a couple of degrees cooler than in the abdomen and the temperature rising may damage fertility. Nevertheless, research in recent decades suggests that the issue of fertility is more complex than a simple matter of temperature. It seems likely that subtle or transient hormone deficiencies or other factors that lead to lack of descent also impair the development of spermatogenic tissue. But there are no known cases of men with PWS fathering a child.

**Prevention**

When the deletion of genes occurs randomly, the condition cannot be prevented. But in small number of cases, a genetic mutation is inherited from father. In these cases, the genetic counseling should be considered. This will help to determine risk of having another child with Prader-Willi syndrome. In cases of deletion in imprinting centre preimplantation genetic diagnosis (PGD) may be an option.

Various diagnostic modalities like testing of DNA methylation test or microsatellite analysis, fluorescence in situ hybridization (FISH) or chromosome microarray (CMA) techniques are prerequisite to undoubtedly confirm the clinical diagnosis of PWS.

**Symptoms**

There are many signs and symptoms of Prader-Willi syndrome depend on age, or organ which is influenced.

**Uterus and birth**
- reduced fetal movement
- frequent abnormal fetal position
- occasional polyhydramnios (excessive amniotic fluid)
- often breech or caesarean births
- lethargy

**Childhood**
- delayed milestones/intellectual delay
- excessive sleeping
- strabismus ('crossed eyes')
- scoliosis (often not detected at birth)
- cryptorchidism (the absence of one or both testes from the scrotum)
- obesity

**Adulthood**
- infertility (males and females)
- hypogonadism
- sparse pubic hair
- obesity
- hypotonia (low muscle tone)
- learning disabilities/borderline intellectual functioning (but some cases of average intelligence)
- prone to diabetes mellitus
- extreme flexibility

**Physical appearance**
- prominent nasal bridge
- small hands and feet with tapering of fingers
- soft skin, which is easily bruised
- excess fat, especially in the central portion of the body
- high, narrow forehead
- thin upper lip
- downturned mouth
- almond-shaped eyes
Therapies

Self therapy

Physical Activity

Physical activity and sports are a fundamental therapy for PWS patients.

During childhood, physical activity improves physical functions, promotes socialization, helps improve caloric expenditure, together with diet, is one of the best ways to limit access to food.

We suggest regular daily physical activity of around 30 minutes. Any kind of sport is possible, and parents should consider the abilities and tastes of their children when choosing.

Although hypotonia improves with age, it persists into adulthood, together with reduced muscle mass.

Dietary Control

Incorrect eating is one of the most serious disorders affecting the lives of children and adults with PWS. Hyperphagia is a serious chronic problem for children with PWS, together with their families, and it can severely limit independence in adult life due to the risk of life-threatening obesity.

Controlling food-related behavior is complex, aiming to limit the child’s access to food, reduce exposure that can cause the child to think about food, and promote a daily routine that helps obtain good weight control. Relatives and friends also have to understand that “sneaking” food to the child with PWS is not a demonstration of affection as, on the contrary, it undermines the child’s nutritional regimen and sense of wellbeing.

Conventional medicine

Pharmacotherapy

Psychotropic drugs

In adolescence and adulthood some patients develop psychosis that requires pharmacological treatment. In experience, it is advisable to start treatment with psychotropic drugs at low doses, due to the possible hyper-responsiveness or paradoxical effects induced by commonly used. The drugs used are benzodiazepines, classical antipsychotics and atypical antipsychotics, mood stabilizers, and selective serotonin reuptake inhibitors. Molecules lacking orexigenic action, or with a lower capacity to induce increased appetite, such as risperidone and fluoxetine, are preferable. Topiramate might help combat the skin-picking phenomenon (Pic.4).

Surgical therapy

Scoliosis surgery

Surgical treatment is indicated in severe early-onset scoliosis-kyphosis, and in adolescents near skeletal maturity. Due to the possibility of complications, surgical treatment requires a multidisciplinary team with expertise in the management of scoliosis and PWS.

Assisted reproduction

Assisted reproductive technology (ART) is the technology used to achieve pregnancy in procedures such as fertility medication, artificial insemination, in vitro fertilization and surrogacy. It is reproductive technology used primarily for infertility treatments, and is also known as fertility treatment. Some forms of ART are used with regard to fertile couples for genetic reasons (preimplantation genetic diagnosis,
Among women with older reproductive age, with history of repetitive abortions or genetic disorders, genetic analysis is highly recommended. The PGS (pre-implantation genetic screening)/PGD allows studying the DNA of eggs or embryos to select those that carry certain damaging characteristics. It is useful when there are previous chromosomal or genetic disorders in the family, within the context of in vitro fertilization programs.

Patients suffering from Prader-Willi syndrome does not utilize techniques of assisted reproduction. Most of these patients are no capable of take care of themselves and require 24 hours custody.

Find more about related issues

Diagnoses

Non-obstructive azospermia
Complete absence of sperm in the ejaculate due to testicular failure.
Learn more at: www.fertilitypedia.org/therapy/diag/non-obstructive-azoospermia

Therapies

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation

ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: www.fertilitypedia.org/edu/therapies/icsi

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilitypedia.org/edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: www.fertilitypedia.org/edu/therapies/standard-ivf

Gallery
The long-term effects of hypotonia on a child's development and later life depend primarily on the severity of the muscle weakness.

Obese patient with Prader-Willi syndrome, eight years old.

Left the patient at the start of treatment, intermediate result in the middle and final result at 19 years on the right.
PIC
B Straight borders of ulnar side of hands and scars from skin picking. C Active and healing skin lesions on scalp.

Prader-Willi syndrome
Obesity, almond shape eyes, down-turned mouth and straight borders of inner legs.

Short statured Patient with only little overweight according to regular exercising
This 24 year old woman with PWS is short statured, compared to her mother next to her on this picture.