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A REVIEW ON PRADER–WILLISYNDROME: UNDERSTANDING AND MANAGING A COMPLEX GENETIC DISORDER

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Abstract

Prader-Labhart-Willi is another name for PWS, are genetic condition. It affects the brain as well as several body organs. It is caused by the loss of specific genes onchromosome 15 due to paternal deletion, maternal uni-parental disomy/imprinting defect that causes the hypothalamus to disintegrate, and it causes endocrine abnormalities, growth hormone deficiency, hypogonadism, and insufficiency of the central adrenal gland. About 1 in 30,000 persons worldwide, including men and women, suffer from PWS, which is characterized by poor feeding, hypotonia in infancy and obesity, intellectual disability, and low sex hormones in childhood. Anearlydiagnosis of PWS is detected (DNAmethylationtest) as early as possible for better results, which can enhance quality medical care.

Keywords: Prader-willisyndrome, chromosome15, uniparentaldisomy, endocrine abnormalities, hypogonadism, hypotonia, obesity.

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Introduction

In the year 1956, PWS was first identified by three Swiss doctors: Prof. . Andrea Prayer, Dr. Alexis Labhart, and Dr. Heinrich Will. It is a rare and complex multisystem genetic disorder characterized by anomalies on chromosome 15, which impair growth, metabolism, hunger, and behavior.Moreover, it may result in impulsive skin picking. The main symptoms include that poor muscle tone, learning deficits, fatigue, sleep disturbances, growth hormone deficiency, motor skill, and speech difficulties, anxiety, increased appetite, and obsession with food lead to obesity if the diet is not closely monitored. The development of low stature occurs during childhood. Newborns may experience hypotonia due to feeding problems. People with PWS exhibit eyes that are almond-shaped, a narrow forehead in appearance, a downturned mouth with a triangular shape of the upper lip, and small hands and feet. There is currently no cure for this illness, although complications like type 2 diabetes, intellectual disabilities, and infertility have been reported. Results are enhanced by supportive care, hormonal treatments, and medications.

Etiology

This multisystem disorder is caused by malfunctions in genetic material, which are paternally inherited genes from the chromosome 15 q 11-q13 region. In general, people normally inherit the identical gene on the paternal copy within the proximal arm of chromosome 15 and therefore from the maternal copy of chromosome 15, and thus the paternally inherited gene is expressed to give a normal phenotype. This process is termed as imprinting. The maternally inherited genes are normally inactive or silenced, and this process is termed an epigenetic process.

In PWS, the genes in chromosome 15 aren't expressed because these genes aren't transcribed to mRNA.

The gene SNRPN (small nuclear ribonucleoprotein-associated protein N) and cluster of SnoRNAs (small nucleolar RNAs), which are present in chromosome 15, that's related to the PWS region, are involved in the formation of spliceosomes.

There are 3 ways in which these paternal genes wouldn't be expressed.

1. 70% of PWS patients occur because the genes that are inherited from the father will not get expressed because of microdeletion of the paternal gene (father), and therefore the maternal genes are silenced when methyl groups get attached to DNA. The loss of gene OCA2 (formerly called P gene) produces a pigment called melanin that gives a color to the eye, hair, and skin. People with the deletion of OCA2 can have a light complexion, and this cause isn't identified with genetic testing by a process called amniocentesis.

2. 25% of PWS patients are caused by maternal uniparental disomy (UPD), and in chromosome 15, the 2 copies are derived maternally, which are silenced and undergo an error of non-disjunction during meiosis -1.
3. 3% of PWS patients are caused by a mutation within the imprinting center.Due to this imprinting problem, genes on chromosome 15 from father are silenced through DNA methylation. While if there's no imprinting center defect, methylation occurs sometimes, and this process is termed epimutation
4. Rarely, PWS can also be caused when part of a chromosome is transferred to another chromosome by the process of translocation. This translocation causes a missing of a specific group of snoRNA genes known as the SNORD 116 cluster.

Mainly, PWS are 2 types:

1. Atypical PWS: people are diagnosed with PWS, but there are no physical characteristics that mean they are taller than people with PWS, and there's no deficiency of growth hormone.
2. Acquired PWS: PWS symptoms are acquired when there is damage or improper functioning of the hypothalamus. During this situation, an individual doesn't have any genetic abnormalities, but there are a few PWS physical features.

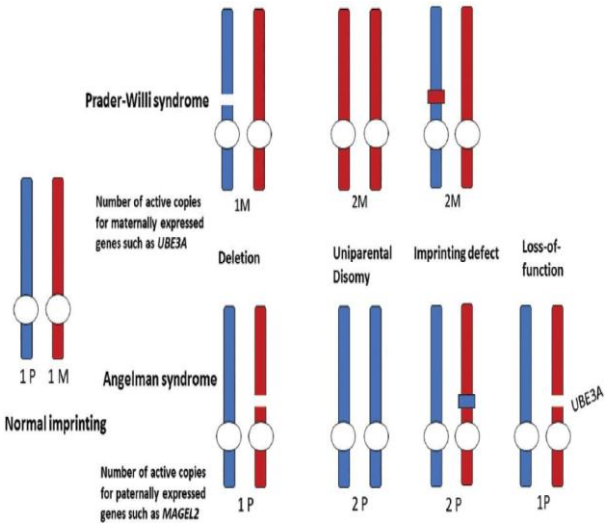
In this acquired PWS management techniques are helpful.

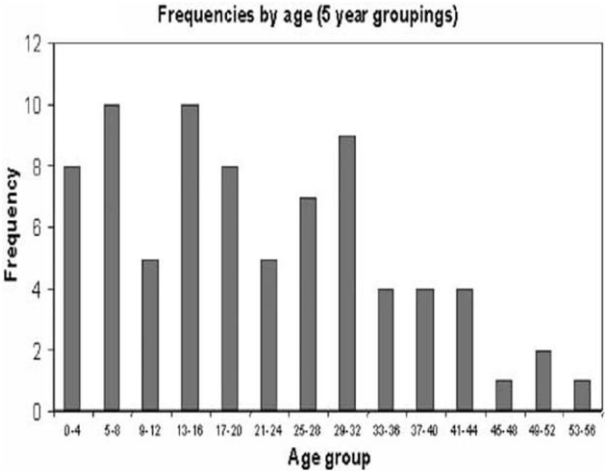
Disorder Associated With PWS

This PWS is similar to a genetic disorder, which is called ANGELMAN SYNDROME. It is caused by the UBE3A gene in chromosome 15 and is called ubiquitin protein ligase. These patients have mental retardation, ataxia, seizures, and inappropriate laughter. Due to these conditions, they have been referred to as "happy puppets."

Epidemiology

Mostly, the PWS cases occur sporadically. PWS occurs with an estimated prevalence worldwide in the ranges of 1 in 10,000 to 30,000 individuals in the general population and about 350,000- 400,000 individuals and is characterized by poor feeding and low muscle tone in infancy and childhood, which causes overeating, intellectual disability, and low sex hormones. It also affects both genders equally; there is no difference between races and ethnicity.

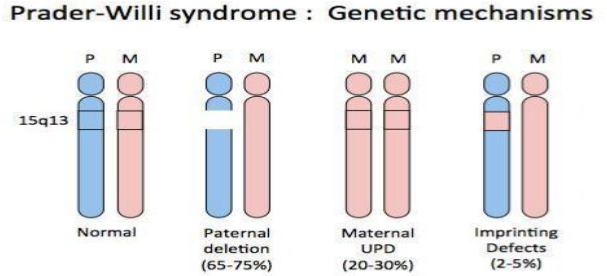




In the U.S., the rate of prevalence has been reported between 1 in 16,062 and 1 in 25,000. Outside of the U.S., reported 1 per 8000 in rural Sweden to 1 per 16000 in western Japan. People with PWS, Between 1973 and 2015, 486 deaths are reported; there are 263 from males, 217 from females, and 6 unknown.

Pathophysiology

PWS is closely associated with a genetic disorder, Angelman syndrome. In both disorders, chromosome 15 is involved. Angelman syndrome is mainly caused by the loss of the UBE3A gene, which is derived from the maternal chromosome. In PWS, loss of seven genes on chromosome 15 is unexpressed, which are derived from the paternal chromosome. Generally, the PWS is not inherited; it develops from genetics during the process of gametogenesis.



The genomic imprinting is the main causative factor in these two syndromes these paternal genes are wouldn't be expressed by few reasons:

1. Deletion

Genes on maternal chromosome 15q 12 are imprinted or silenced, and from the paternal chromosome the functional gene was obtained. When there is missing genetic information by the cause of deletion, the person develops PWS.

2. Maternal-uniparental disomy (2 copies from mother)

The two copies of chromosome 15 that are inherited from mother then the seven PWS genes are methylated and therefore silenced.

3. Mutation in the imprinting center

Both maternal and paternal genes are silenced.

Signs & Symptoms

NEW BORNS (2 months of age)

- Weak muscle tone (hypotonia)—presented at birth or early in life and feels like a "floppy"
- facial abnormalities like: eyes are almond-shaped, forehead and bridge of the nose become narrow, thin upper lip.
- Poor suckling reflex makes it harder to require milk and may result in failure to thrive.
- Poor responsiveness: poor response to stimulation
- Male babies and female babies may have underdeveloped genital organs.
- LATE INFANCY (1 year old)
- Insatiable appetite (they feel unsatisfied even with a full stomach).

Childhood to Adulthood

- Excess weight gain
- Hip dysplasia
- Scoliosis

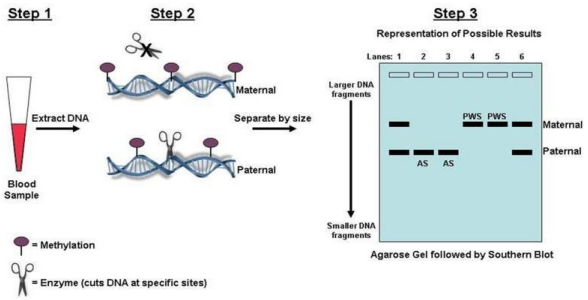
Morbidly obese condition this obese condition leads to complications such as:

1. Type 2 diabetes
2. Obstructive sleep apnea

- Delayed motor development
- Low IQ levels
- Psychotic behavior—particularly people with chromosome 15 UPD
- Insufficiency of central adrenal glands
- Delayed puberty
- Imbalance of Growth hormone can results in short height.

Diagnosis

The diagnosis is confirmed by a blood test method. For detection of this,the PWS methylation test is preferred.



Based on patient history and clinical examination, symptoms are crucial for diagnosis.

• PWS is diagnosed mainly through genetic testing. 99% of cases of PWS are diagnosed with simple molecular tests and DNA-based methylation. This DNA methylation test mainly targets the materially imprinted PWS gene (SNURF-SNRPN) promoter.

• Deletion of paternally inherited genes within the chromosome 15 occurs in 70% of people who are diagnosed by using fluorescence in situ hybridization (FISH) probes. This fish probe identifies a deletion and translocation of chromosome 15.

• UPD can be diagnosed with the help of DNA polymorphism analysis by using informative microsatellite markers from the PWS.

• The test, which is called methylation-specific multiplex ligation probe amplification
(MS-MLPA), was done to rule out the methylation test of an imprinted region.

• High-resolution chromosomal analysis (HRCA) This test is used to identify the typical chromosomal deletion and also detect maternal disomy 15.

• Imprinting defects can be identified by only DNA methylation tests.

Treatment

There is no cure for PWS, but most of the studies have been focused on treating specific symptoms.

Patients with PWS need multidisciplinary care. Symptomatic treatments can improve outcomes and good health care. Detecting symptomatic patients as early as possible for better results.An early diagnosis is important for better results. Physical activity is the main therapy for PWS patients to improve physical functions and promote socialization.

Researchers found that approximately 80% of children with PWS are growth hormone deficient, so ultimately growth hormone therapy is needed for PWS patients to improve their behavior, fat- free mass, height, mobility, and good health care system.

In June 2000, growth hormone therapy was approved by the US (FDA) for the cure of pediatric patients that are diagnosed with PWS, failure to thrive.

Earlier initiation of growth hormone therapy is recommended at 3 months of age.

Starting dose: 0.5 mg administered subcutaneously daily.

Contraindication: active malignancy, severe obesity, and respiratory impairment.

Medications and Care

Hypotonia

During infancy the primary concern is ensuring nutrition and growth, for babies who're not able to breastfeed and often need tube feeding instead for sustenance purposes due to feeding challenges encountered by newborns with an enteral tube inserted through their mouth to the stomach to facilitate feeding properly and efficiently while young children benefit from engaging in regular physical activity and following a balanced diet that is low in calories as a preventive measure, against obesity.

Overweight

Continuous food cravings result in fast weight gain, so the management of weight is necessary through nutritional counseling.

Hypogonadism

Testicular dysfunction in PWS males is common and requires treatment that is recommended by an endocrinologist. In infancy, treatment of HGH, which is known as somatropin, is relatively safe.

Due to an immature sexual development, it is treated with the replacement of sex hormones, which produce secondary sexual characteristics.

Facial features

Eye abnormalities in PWS such as strabismus should consult an ophthalmologist.

Developmental disability

Children with groups of specific behavioral features should need developmental-adapted physical education and social skills training.

Orthopedic problems

Patients with PWS may develop bone fragility, thus use dual-energy X-ray absorptiometry to track the bone density scan.

Supplementing with calcium and vitamin D is advised to treat osteoporosis and osteopenia.

Behavior and psychiatric problems

Behavioral problems and counseling programs are important for PWS patients; they can be treated by parents, teachers, and pediatricians. The person with anxiety is treated with psychotropic medications at low doses

RISPERIDONE is used to treat behavioral disturbance of PWS. DOSE: 0.25, 0.5, 1, 2, 3, 4 mg tablets)

RECOMMENDED DOSE: 0.25 mg/day orally

- Selective serotonin reuptake inhibitors can assist teenagers and adults deal with emotional problems.

Selective serotonin reuptake inhibitors CITALOPRAM DOSE: (10, 20, 30, 40 mg tablets)

RECOMMENDED DOSE: Initially 5 mg/day orally

FLUXOETINE DOSAGE

10 milligram tablet (scored) 20 milligram capsule and 40 milligram capsule. RECOMMENDED DOSE: Start with an dose of 5 milligrams as advised initially. PAROXETINE DOSAGE Options include Tablets in 10MG to 40MG Strengths. RECOMMENDED DOSE: Initially, 5 mg/day orally.

SERTRALINE DOSE: (25 mg scored tab, 50 and 100 mg tabs)

Recommended Dose: Initially, 12.5 mg per day orally.

N-acetyl cysteine/topiramate reduces the skin pricking phenomenon.

Prevention

In general, there is no prevention for PWS because it is a genetic disorder, but it is possible to prevent side effects with treatment. When deletion of genes occurs randomly, this condition is not prevented, but in a few cases, genetic counseling should be needed when mutation of a gene is inherited from the father. This genetic counseling will help to determine the threat of having another child with PWS.

Conclusion

This neurogenetic disorder mainly develops hyperphagia during the initial stage of infancy, and this condition leads to obesity and its complications. Behavior and psychiatric problems mostly in adulthood are detected early and treated. The several problems that are associated with PWS patients require early treatment with growth hormone, and it has a positive effect. Counseling is provided for early-onset obesity.

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Informed Consent

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Ethical Statement

Not applicable

Author Contribution

All authors are contributed equally.

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