Prader-Willi Syndrome (PWS) — Diagnosis and Treatment

Prader-Willi syndrome (PWS) is an unusual, rare complex autosomal neurodevelopmental disease resulting from genomic imprinting and uniparental disomy of maternal chromosome 15 with a simultaneous functional loss of the parental part 15q11.2-q13. This article briefly elucidates the phenomenon of genomic imprinting, focuses on the diverse clinical features of PWS and concludes with the management of the same.

Definition of the Prader-Willi Syndrome

PWS is a rare neurodevelopmental genetic disorder in which 7 genes on chromosome 15 are deleted or unexpressed on the paternal chromosome. The literature points to the hypothalamus, a minute organ of quintessential significance in the regulation of the internal milieu of the body; to be the organ of primary damage. The secondary changes that follow affect a multitude of organ systems in varying proportions. Exact unequivocal evidence to point causation of hypothalamic dysfunction secondary to genetic changes on chromosome 15 eludes us.

PWS is associated with some characteristic symptoms such as obesity, short stature, small hands and feet in physical appearance with diminished fetal activity, hypotonia, hypogonadotropic hypogonadism and mental retardation.
History of the Prader-Willi Syndrome

PWS is variously known as Labhart-Willi syndrome, Prader’s syndrome, Prader-Labhart-Willi-Fanconi syndrome.

It was first divulged in 1956 by Andrea Prader, Heinrich Willi, Alexis Labhart, Andrew Ziegler, and Guido Fanconi of Switzerland. Some equivocal evidence points to a description of similar illness by Langdon Down way back in 1887.

Epidemiology of the Prader-Willi Syndrome

The prevalence of PWS is about 1 in 15,000 to 1 in 30,000 live births. There is no sex discrimination seen in the natural course of the illness. It is a genetic disorder that remain throughout the life.

Genomic Imprinting and Prader-Willi Syndrome

In genomic imprinting, genes are expressed in a parent of origin-specific manner. Chromosome 15 contains a genomically imprinted region. Genes are expressed only on the paternal and maternal chromosomes. Each region is hypermethylated (imprinted/turned-off) on the opposing chromosome.

PWS patients have a double dose of maternal chromosome 15 q segment (uniparental disomy) or absence of paternal homologous segment (microdeletion). Non-disjunction in meiosis I lead to heterodisomy and isodisomy. In an attempt to rescue the cell from trisomy; the paternal chromosomal segment is eliminated in heterodisomy. The result is uniparental disomy of maternally derived chromosome 15 segment.

As a consequence of genomic imprinting; only paternal copies of these genes are expressed and maternal alleles even if present are innately functionally silent. Precisely; about 70 % of cases are a culmination of deletion of the paternal chromosomal segment; while the remaining cases are accounted by maternal uniparental disomy. The latter have 2 copies from the mother and none from the father. The end result of both these circumstances is an absence of working copies of about 7 genes as parts of maternal chromosomes are inactive by default and require the paternal counterpart to function.

Essentially, loss of paternal copies of SNRPN, necdin genes and the clusters of snoRNAs: SNORD64, DNORD107, SNORD 108, 2 copies of SNORD116, 48 copies of SNORD115 results in PWS syndrome. These are the constituents of the “PWS/AS region”. Human and experimental mice studies have pinned down deletion of the 29 copies of the C/D bos snoRNA SNORD116 (HBII-85) as the predominant critical cause of PWS. There are different mechanisms by which this functional loss occurs. The same can be summarized in short as follows:

- Chance mutation deletion and microdeletions
- Uniparental disomy
- Sporadic mutation
- Chromosome translocation
- Gene deletion

The similar process when reversed; the existence of 2 copies from the father and none from mother result in Angelman syndrome (AS).
Clinical Features of the Prader-Willi Syndrome

The hypothalamus seems to be deeply affected in PWS patients. Hypothalamus is the minuscule endocrine master at the base of the diencephalon that is indispensable in the regulation of the multitude of essential bodily functions like hunger and satiety, temperature and pain regulation, fluid balance, puberty, emotions, and fertility.

Evidence attests to the fact that normal functioning of the hypothalamus is hampered by chromosome 15 abnormalities. The hypothalamic **arcuate nucleus** regulates appetite. Also, hypothalamic **oxytocin** producing cells which under usual circumstances monitor satiety are abnormal in these patients. Lastly, exorbitant **ghrelin** levels in these patients are hypothesized to be culpable for obesity, hyperphagia and the voracious appetite.

There are 2 generally recognized stages of the symptoms associated with PWS:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Infants are hypotonic or “floppy” with very low muscle tone. Weak cry and a poor suck reflex are typical. Babies with PWS usually are unable to breastfeed and frequently require tube feeding. Failure to thrive if feeding difficulties are not monitored and treated. Strength and muscle tone generally improve. Motor milestones are achieved but are usually delayed.</td>
</tr>
<tr>
<td>Stage 2</td>
<td>It is characterized by a voracious appetite. The absence of normal satiety and hunger cues is characteristic. This stage is encountered between 2-6 yrs of age. Obesity, overeating, and food seeking behavior are prevalent. If left untreated, frank obesity with its subsequent ill complications like Type 2 Diabetes mellitus often sets in. The lower basal metabolic rate is present.</td>
</tr>
</tbody>
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Other characteristics of PWS patients can be summarized as follows:

- Diminution of sex hormone levels with reduced fertility
- Musculoskeletal developmental delay with late development of motor finesse
and speech
- These patients have characteristically narrow forehead with small short limbs with delayed puberty growth
- Behavioral issues to a sudden change in surroundings with frequent temper tantrums
- Skin picking
- Learning disabilities
- Perseveration of speech and repetition
- Mental retardation, low IQ. Some children can have normal intelligence
- Abnormal behavioral traits like collecting possessions
- Sleep disorders like obstructive sleep apnea

Some patients with PWS have some remarkable cognitive skills like jigsaw puzzle solving.

PWS has a diverse range of symptoms and signs which mature with the patient. In 1993 Holm et al described a specified set of symptoms and signs as pretest indicator of PWS. They are segregated as per age and can be described in short as follows:

<table>
<thead>
<tr>
<th>Age cohort</th>
<th>Symptoms and Signs</th>
</tr>
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<tbody>
<tr>
<td>Inutero</td>
<td>Diminished fetal movement, aberrant fetal presentation, and lie, prevalent polyhydramnios</td>
</tr>
<tr>
<td>At Birth</td>
<td>Hypotonia, and feeding difficulty are the characteristic features. Breathing difficulty, lethargy, and hypogonadism also co-exist frequently</td>
</tr>
<tr>
<td>Childhood</td>
<td>Hyperphagia, insatiable craving for food, weight gain, obesity and its complications such as Obstructive sleep apnea and Type II Diabetes mellitus. Scoliosis, strabismus, speech delay, cryptorchidism, delayed puberty and intellectual retardation are also encountered.</td>
</tr>
<tr>
<td>Adulthood</td>
<td>Borderline intellectual capability, extreme flexibility secondary to diminished but persistent hypotonia, hypogonadism and infertility raise suspicion for PWS in adults.</td>
</tr>
</tbody>
</table>

PWS affects multiple organs in magnitudes of variable severity.

The symptoms could be classified as per the organ system affected as follows:

<table>
<thead>
<tr>
<th>Organ system inflicted</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical morphology and musculoskeletal system</td>
<td>Almond-shaped eyes, striae, bruised picked skin, central adiposity, dysmorphism, depigmentation in the skin small limbs and the conspicuous absence of sexual development.</td>
</tr>
<tr>
<td>Neuro-cognitive system</td>
<td>Based on their research in the neuropsychological development of PWS individuals, Curfs and Fryns in 1992 concluded that majority; about 39 % of patients have a mild intellectual disability with IQ of about 50-70; while only about 5 % of patients had high to low average intelligence. About 2 % of patients had dismal IQ scores below 35. Auditory data retrieval, cognition and response formulation; visual attention span, writing skills and executive task management are all affected.</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>Short stature, obesity, hypogonadism, undescended testes and benign premature adrenarche in females are the key issues. Early detection can help in treatment and even prevention of some these situations.</td>
</tr>
<tr>
<td>Ophthalmologic involvement</td>
<td>Strabismus and esotropia are commonly seen</td>
</tr>
</tbody>
</table>

Diagnosis of the Prader-Willi Syndrome

While earlier medical personnel relied mainly on clinical features; the current trend is to use clinical features based on the first impression to suspect PWS. This is mainly in patients with hypotonia and then confirm the same with modern genetic testing armamentarium. Different cytogenetic analysis techniques can be implemented to diagnose PWS.

Some of the most commonly used ones can be summarized as follows:

<table>
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<tr>
<th>Technique</th>
<th>Explanation</th>
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FISH (fluorescence in situ hybridization)

Using fluorescence microscopy and fluorescent probes; FISH determines presence or absence of specific DNA sequences on the chromosomes of interest. It is instrumental in defining the specific spatiotemporal gene profile in cells and tissues in PWS patients. It can be used to detect prenatally the deletion in the 15q region after amniocentesis or chronic villus sampling.

Methyl collector Ultrafast magnetic assay for specific isolation of CpG-methylated DNA

DNA methylation is critical in the regulation of gene expression in the multitude of cellular functions. This assay, albeit expensive, delivers capability to isolate methylated CpG segments from mammalian DNA of interest. In PWS patients; absence of paternally derived 15q11-q 13 segments diagnosed about 97% of cases. This test is offered to an infant with marked hypotonia.

Management of the Prader-Willi Syndrome

A circumferential multifaceted integrated approach is a prerequisite when one yearns to manage PWS.

To ensure an independent future, the important elements to focus on can be summarized as follows:

- Speech therapy
- Exercise
- Physical activity management
- Behavioral therapy
- Hormone replacement therapy
- Medical therapy with drugs

Parental counseling and education are equally important. They need to understand the disease; their offspring and then decide on a management plan. Indeed, simple measures like keeping the fridge locked and close scrutiny of food in the house can go a long way.

At present, human Growth hormone (HGH) is the only FDA-approved hormonal supplement which has evident benefits in the management of PWS.
Some of the established benefits can be enumerated as follows:

- Increment of bone mineral density
- Improvement in stamina
- Height increase
- Generalized improvement in body ratio and weight distribution
- Diminution of body fat with simultaneous improvement in muscle mass

The areas of active research in PWS which still seeks answers can be summarized as follows:

- Psychiatric issues like behavioral trouble to adjust to new surroundings and temper tantrums
- Regulation of appetite
- Control of food intake
- Learning disabilities
- Mental development

Prognosis of the Prader-Willi Syndrome

Active care to prevent obesity and its untoward consequences can often ensure normal lifespan. Cognitive problems are common. No cure at present is available. Behavioral counseling and testing can be rendered to the afflicted families. Group homes form an effective strategy in adults.

Recent Advances of the Prader-Willi Syndrome

Some new fascinating therapies are underway in research and development to tap their true potential against PWS.

The relevant ones can be summarized as follows:

- Bariatric surgeries like a gastric bypass to abridge obesity and its subsequent complications
- Surgical treatment of cryptorchidism and scoliosis
- Tonsillectomy, adenoidectomy or tracheostomy placement for obstructive sleep apnea
- Beloranib: drug to regulate weight and appetite
- Serotonin agonists to improve impulse behavior have proved to be very effective
- Positive airway pressure machine as many PWS patients also have obstructive sleep apnea

Genetic Testing and Counseling of the Prader-Willi Syndrome

Prenatal genetic testing should be offered to families with PWS inflicted children to determine the risk to the future offspring. Interestingly; even though the roots of this syndrome are traced back to chromosomes; this is not a genetic disease in the strict terms as it is not hereditary. The genetic damage occurs during meiosis, the formation of the haploid gametes or in early development. These changes that lead to the genetic aberration are often spontaneous though sporadic. Thus; the risk estimate depends on
the involved genetic aberration that occurs in the first place and can vary grossly accordingly.

When the aberration takes place in the imprinting control region and is likely to be replicated in the future offspring; PWS often behaves as autosomal dominant disease. The risk to the next sibling is almost up to 50% then. The future sibling is prone up to 1%; similar to the normal population if the affected individual has uniparental disomy or a gene deletion. This risk escalates to about 25% when the cause is a parental chromosomal translocation. These statistics can be inferred from prenatal genetic testing for determining the underlying genetic mechanism.

Summary

Prader-Willi syndrome (PWS) is an unusual autosomal disease where loss of paternal alleles or duplication of maternal copies of chromosome 15 q11.2-q13 segment leads to loss of function secondary to genomic imprinting functional in this region. The reverse leads to Angelman syndrome.

PWS involves multiple organs as secondary consequence which can’t be reversed but can be managed medically or surgically.

Hypothalamus is the hypothesized organ primarily inflicted in PWS. The subsequent implications of hypothalamic dysfunction are evident in almost every organ system of the body. The key concerns are feeding difficulties and hypotonia in infancy, while in children and adults hypogonadism, impulsive eating, and behavioral issues are most evident.

PWS was; until recently a clinical diagnosis. We now are equipped with genetic testing like FISH and tests to detect hypermethylation to accurately diagnose PWS.

There are many ways a PWS patient can be assisted to enhance independent living. Complete cure, unfortunately, is yet to be discovered.

Genetic testing and counseling can be offered for risk estimation of potential infliction of future generations and siblings of patients with PWS.

Review Questions

The correct answers can be found below the references.

1. Which of the following describes the chromosomal abnormality in Prader-Willi syndrome patients?
   A. Uniparental disomy of maternal 15 p11.2-q13 segment
   B. Uniparental disomy of paternal 15 q11.2-q13 segment
   C. Uniparental disomy of maternal 15 q11.2-q13 segment
   D. Uniparental disomy of paternal 15 q11.2-p13 segment

2. Which of the following diagnostic method are used in diagnosing patients with Prader-Willi syndrome?
   A. Sperm-hamster egg penetration studies
   B. Karyotyping
   C. Barr body studies
   D. FISH studies.

3. Which of the following hormone therapy is FDA approved for Prader-Willi
syndrome patients?

A. Testosterone
B. Human growth hormone
C. Thyroid hormone
D. Prolactin.

References


Nelson’s textbook of Pediatrics.


Correct answers: 1C, 2D, 3B

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