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Prader–Willi Syndrome: Clinical Features, Diagnosis, and Therapeutic Approaches”

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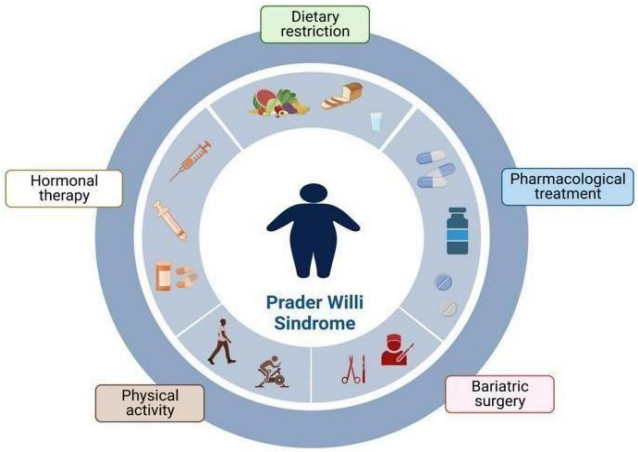
ABSTRACT:

The most frequent genetic cause of syndromic obesity is Prader-Willi syndrome (PWS), a rare neurogenetic illness caused by loss of expression of paternally inherited genes on chromosome 15q11–q13 because of maternal uniparental disomy, paternal deletion, or imprinting abnormalities. About 1 in 10,000 to 30,000 live births are affected by it. Age-dependent characteristics of PWS include hypotonia, poor eating, and failure to thrive in infancy, followed by cognitive impairment and developmental delay. Hypothalamic dysfunction in early childhood causes obesity, excessive food-seeking behavior, and hyperphagia. Short stature, hypogonadism, behavioral issues, and endocrine disorders such growth hormone insufficiency are other characteristics. DNA methylation analysis is used to confirm the diagnosis. Survival and quality of life are enhanced by early interdisciplinary care.

KEY WORDS: Genetic disorder, Chromosome 15q11–q13, Paternal gene deletion, Genomic imprinting, Hypothalamic dysfunction and Neonatal hypotonia.

Introduction:

Prader Willi Syndrome is the most common cause of genetic obesity. It’s a rare genetic disorder. The First described in 1956. About 74% of cases occur in father chromosomes 15 are deleted. It is characterized by an insatiable appetite. PWS, which affects one in 25,000 births, affects. PWS is recognized by microdeletion syndrome identified by high resolution chromosomes analysis. In PWS chromosomes 15q11-q13, most commonly due to paternal deletion. PWS is affected by Uniparental disomy [UPD] in the region of chromosomes 15. PWS review focuses on a benefit that is a multidisciplinary approach to children. In babies' symptoms include weak muscles, poor feeding, and slow development. The syndrome presents severe neonatal hypotonia, progressive hyperphagia, and development of life-threatening obesity in childhood.



REVIEW OF LITERATURE:

Merlin G Butler et.al The literature describes PWS as a rare neuro development genomic imprinting disorder caused by the absence of expression of paternally inherited genes in the chromosomes 15q-11q13 region. The most cases are paternal deletions (60%), and maternal uniparental disomy 15 (35) less affected by imprinting center defects. Clinical literature consistency reports severe neonatal hypotonia, poor suck and hyperphagia endocrine dysfunction in early childhood hyperphagia. Obesity-related complications are primary contributors to morbidity and mortality in PWS. The importance of early and accurate genetic diagnosis, identification of specific genetic subtypes

EU-Seno Noh. Min Sankim et.al Prader Willi Syndrome is a rare genetic disorder characterized by an insatiable appetite that leads to morbid obesity. PWS studies on younger adults are lacking. The prevalence of endocrine and metabolic illnesses compared with those an age, sex and BMI matched healthy control group. The PWS group that maintained recombinant human growth treatment in adulthood had a lower probability of BMI.

Victoria E Goldman et.al PWS has a high obesity rate due to hyperphagia and decreased metabolic rates. Disruption in hormones regulating food intake. Reduced energy expenditure because of hypotonia. Current treatment for obesity in PWS includes growth hormones. Topiramate is medication that blocks sodium and calcium channels inhibitory effect GABA that initiation of these anti-obesity medications (AOMs) can be combination treatment with dietary limitation and increase exercise at home. obesity is leading cause of mortality and high morbidity rates among individual with PWS 3%annuval death rate across all age 47,48,49. AMOs for the indication of weight management.

Maithe Tauber, Muriel coup aye et.al It was hypothesized that hyperghrelinemia would explain at least a part of the feeding behavior and body composition of PWS patients, who are characterized by hyperphagia an obsession with food and food seeking and increased adiposity. PWS was first reported in 1956 by Prader, Lab Hart and Willi as genetic multisystem disorder with eating disorder hormone deficiency, cognitive impairment, intellectual deficits and behavioral disorder.

Pankaj K. Gadhia, Salil N. Vaniawala et.al The prevalence of PWS was studied using both classic cytogenetics and Fluorescence in situ hybridization(fish) technique in referred cases of microdeletion 15q11-13 to our laboratory from western India. PWS is a complex multisystem disorder due to the absent expression of the paternally active genes in the PWS region on chromosome. In 75 to 80% of affected individual there is a microdeletion of paternal chromosome 15q11-13.the differential diagnosis includes obesity, cryptorchidism, short stature, mental retardation, sleep apnea and squint myopia. A total of 53 patients clinically diagnosed as PWS were referred to us for a chromosome study and 23 analyses.

AIM AND OBJECTIVES:

Aim: The aim of this review is to provide a comprehensive overview of Prader–Willi syndrome, focusing on its genetic basis, epidemiology, pathophysiology, clinical manifestations, diagnostic approaches, complications, and current management strategies, with an emphasis on the importance of early diagnosis and multidisciplinary care to improve patient outcomes and quality of life.

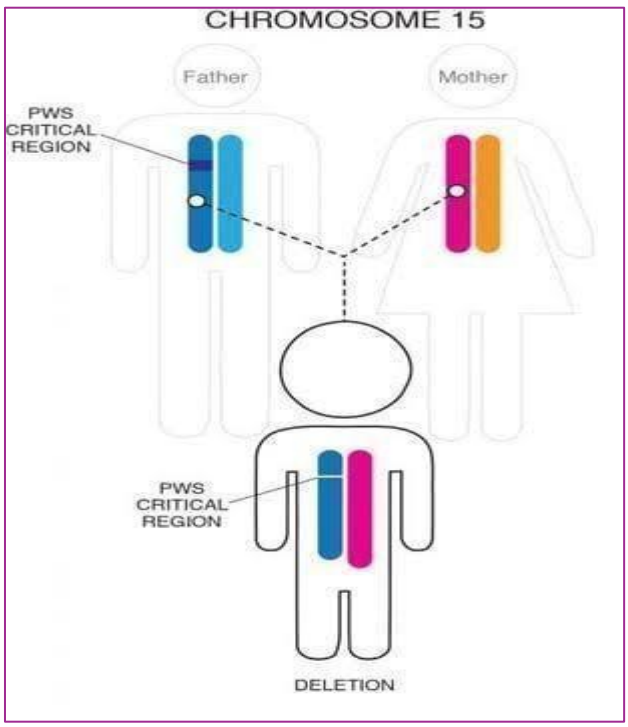
Objectives: This review's main goal is to present a thorough and current understanding of Prader-Willi syndrome (PWS), a rare hereditary condition marked by intricate multisystem interaction. The goal of this study is to provide an overview of the genetic foundation and epidemiology of PWS, with a focus on the main molecular pathways underlying illness development and genomic imprinting errors affecting the chromosome 15q11–q13 region. Presenting up-to-date epidemiological data, the review aims to emphasize the significance of early detection, awareness, and precise diagnosis of this disorder. The review also examines the underlying pathophysiology of Prader-Willi syndrome, emphasizing hypothalamic dysfunction and its effects on growth limitation, metabolic disorders, hunger regulation, endocrine abnormalities, and behavioral abnormalities. The characteristic age-dependent clinical manifestations are outlined, ranging from neonatal hypotonia and feeding difficulties to childhood-onset hyperphagia, obesity, hypogonadism, cognitive impairment, and psychiatric features. In addition, this review evaluates current diagnostic and

management strategies for PWS, emphasizing the role of molecular diagnostic techniques such as DNA methylation analysis. Available therapeutic approaches, including growth hormone therapy, structured nutritional management, behavioral and psychological support, and long-term monitoring for complications, are discussed. Through this comprehensive approach, the review highlights how early diagnosis and lifelong multidisciplinary care can significantly improve clinical outcomes, functional abilities, and overall quality of life in individuals with Prader–Willi syndrome.

ETIOLOGY:

The complicated genetic condition known as Prader-Willi syndrome (PWS) is brought on by the loss of expression of paternally inherited imprinted genes found on chromosome 15q11.2–q13. In the PWS crucial region, only the paternal genes are activated, whereas normally, each parent contributes one copy of chromosome 15. PWS arises when these genes are silent or missing. The 15q11.2–q13 region has a paternal deletion in around 70% of PWS cases; these deletions can be categorized as type I, type II, or atypical. Maternal uniparental disomy (UPD), where both copies of chromosome 15 are inherited from the mother, accounts for about 25% of instances. Microdeletionsor epigenetic alterations that interfere with proper genomic imprinting are examples of imprinting center anomalies that cause rare occurrences. Despite reports of familial occurrences, the majority of cases happen seldom.

The clinical manifestations of PWS include hypotonia, poor eating, and failure to thrive during infancy, followed by behavioral abnormalities, hyperphagia, obesity, developmental delay, and cognitive impairment. Thyroid dysfunction, growth hormone insufficiency, hypogonadism, and central adrenal insufficiency are among the frequent endocrine problems brought on by hypothalamic dysfunction. The significance of parent-of-origin- specific gene expresson was highlighted by the discovery that PWS was the first disorder to be linked to genomic imprinting.



EPIDEMIOLOGY:

Prader–Willi syndrome (PWS) is a rare, complex neurogenetic disorder with an estimated prevalence ranging from 1 in 10,000 to 1 in 30,000 live births worldwide. There is no racial bias because the illness affects both gender equally and is present in all ethnic and geographic groups. PWS is caused by lack of expression of paternally inherited genes on chromosome 15q11-q13, which is most frequently caused by imprinting abnormalities (1-3%), maternal uniparental disomy (20-30%), or paternal deletion (65-75%). Although genuine rates may be overestimated due to delayed diagnosis or under-recognition, particularly in milder phenotypes, the incidence is estimated to be around 1 in 15,000–25,000 newborns. Molecular genetic testing advancements, such as DNA methylation analysis, have enhanced early detection, especially infancy when feeding issues and hypotonia are common.

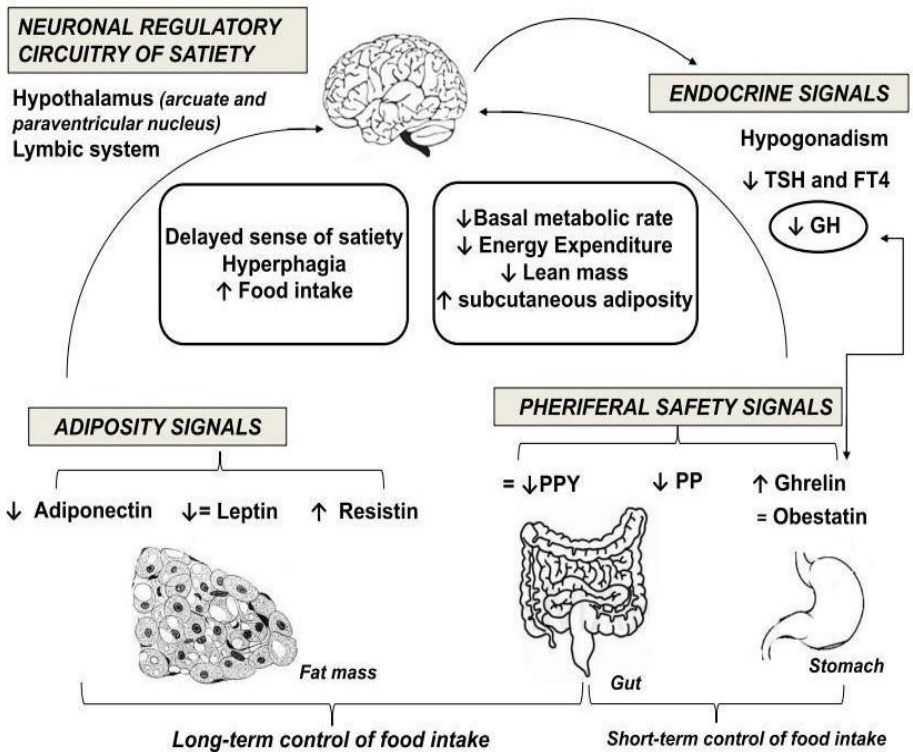
Genetic Epidemiology:

PWS is the absence of expression of paternally inherited genes on chromosome 15q11-q13.

- Paternal deletion of 15q11-q13. (65-75%)
- Maternal uniparental disomy (UPD). (20-30%)
- Imprinting defects. (1-3%)

PATHOPHYSIOLOGY:

Prader-Willi Syndrome (PWS) is a complex genetic disorder from chromosome 15 that affects metabolism, development, and behavior. It is characterized by severe hypotonia (poor muscle tone) and feeding problems in infancy, followed by insatiable hunger (hyperphagia) and obesity from childhood, as well as cognitive delays, learning disabilities, behavioral issues (tantrums, skin picking), hypogonadism, short stature, and distinctive facial features.



Obesity in Prader-Willi Syndrome:

The coordinated control of hunger, fullness, and body weight by gastrointestinal, neurological, endocrine, and adipose cues. The limbic system, adipose tissue, stomach, and endocrine organs provide inputs to the hypothalamus, namely the arcuate and paraventricular nuclei, which serve as the core control center. Disruption of this regulatory circuitry causes fullness to be delayed, which increases food intake and causes hyperphagia. Hypogonadism, low thyroid hormones (TSH and FT4), and low growth hormones are examples of endocrine disorders that lower basal metabolic rates, decrease energy expenditure, diminish lean body mass, and increase subcutaneous fat formation. Reduced adiponectin, inefficient or decreased leptin signalling , and elevated resisting are some of the long-term signals that adipose tissue delivers through adipokines.

Based on genital hypoplasia:

In neonates with PWS, genital hypoplasia is a common finding, occurring in 13 out of 15 cases (86.5%) that were evaluated in order to derive newborn diagnostic criteria.44,105 More than 90% of male babies with PWS have cryptorchidism, with the majority of cases being bilateral.17, 54, 57 Contrary to this, just 5% of infant men who are not PWS have cryptorchidism.19. While the diagnosis and management of retractile and gliding testes are similar, it is crucial from a clinical standpoint to differentiate true cryptorchidism from these diseases. While micro-penis is recorded in less than 50% of PWS cases, small testes and scrotal hypoplasia though typically not a true bifid scrotum is also documented usually. There have been no reports of hypospadias or the preservation of female anatomy.

CLINICAL PRSENTATION:

Prader–Willi syndrome (PWS) is commonly studied in relation to hyperphagia and obesity, growth hormone deficiency, hypogonadism, behavioural problems such as food seeking, small hands, severe hypotonia, weak muscles, poor feeding, and slow development in babies, sleep issue, infertility, insatiable appetite, developmental delays, which can lead to numerous serious complications. These include fatty liver disease, right- sided heart failure, respiratory insufficiency, narrow airways with obstructive sleep apnea, and skin problems such as cellulitis and venous stasis ulcers. Even individuals with PWS who are not morbidly obese may develop gastroparesis and, in severe cases, gastric necrosis with rupture due to excessive food intake. Constipation or gastroenteritis can contribute to gastroparesis. People with PWS often do not respond appropriately to gastric distention or abdominal p ain because of high pain tolerance and an impaired ability to vomit, which increases the risk of unrecognized gastric inflammation or necrosis. In addition, excessive fluid intake, low vasopressin levels with fluid retention, or the use of medications such as diuretics and antidepressants that interfere with electrolyte balance can result in water intoxication and electrolyte abnormalities, including dilutional hyponatremia. Prader–Willi syndrome (PWS) is a complex multisystem genetic disorder characterized by a distinctive, age-dependent clinical phenotype involving neurodevelopmental, endocrine, metabolic, and behavioural abnormalities. The manifestations evolve from infancy through adulthood.

- Prenatal and neonatal period
- Infants and early childhood
- Childhood and adolescence
- Endocrine and metabolic features
- Neurobehavioral and psychiatritric manifestations
- Hypogonadism

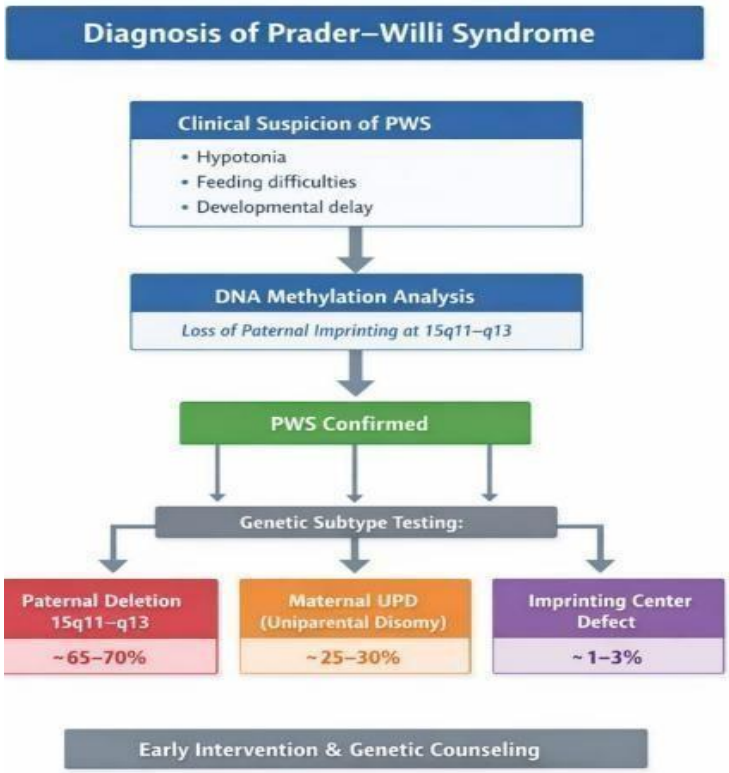
DIAGONSIS:

Prader Willi Syndrome (PWS) causes loss of expression of paternally inherited genes on chromosome 15q11–q13, a rare genetic condition. Severe hypotonia, poor eating, and failure to grow in infancy raise clinical suspicion, later symptoms include developmental delay, hyperphagia, obesity, hypogonadism, and aberrant behaviour. The gold-standard test, DNA methylation analysis, is used to make a definitive diagnosis in almost 99% of instances. Following confirmation, the underlying genetic mechanism—paternal deletion (≈65–70%), maternal uniparental disomy (≈25–30%), or imprinting centre abnormalities (≈1–3%)—is determined using additional genetic tests including chromosomal microarray, FISH, MLPA, or microsatellite analysis. To improve long-term results, early diagnosis is essential for starting growth hormone therapy, dietary control, developmental support, and genetic counselling.

The lack of function of paternally expressed genes in the 15q11–q13 region of chromosome 15 causes Prader– Willi syndrome, an uncommon genetic imprinting condition. It has a unique developmental phenotype that varies with age and impacts several systems.

Types of diagnosis

1. Clinical Features Suggestive of Prader Willi Syndrome
2. Clinical Diagnostic Criteria
3. Molecular Genetic Diagnosis
4. Differential Diagnosis



COMPLICATION:

Prader Willi syndrome lacks expression of paternal genes on chromosome 15q11-q13 results, a complicated, chronic genetic condition. It causes a variety of medical, metabolic, endocrine, neurological, respiratory, gastrointestinal, skeletal, behavioural, and psychiatric issues. It predominantly impacts several physiological systems through hypothalamic dysfunction.

Prader–Willi syndrome (PWS) is a complex multisystem genetic disorder characterized by hypothalamic dysfunction, resulting in a variety of endocrine, neurodevelopmental, metabolic, medicinal, and psychological issues. These issues evolve with age and are a major cause of morbidity and a lower standard of living.

- Metabolic and Nutritional complications
- Endocrine complication
- Respiratory and Sleep complication
- Gastrointestinal complications
- Neuropsychiatric and behavioural complications
- Skeletal and muscular complications
- Cardiovascular complications

TREATMENT:

A rare genetic condition, Prader-Willi syndrome is thought to affect 1 in 15,000– 30,000 live births. The clinical symptoms affect several organ systems and change as people age. Uncontrolled hyperphagia causes morbid obesity and related metabolic problems, which are the most serious consequences. Physical, cognitive, and psychosocial outcomes have been demonstrated to be much improved by early and thorough management. Multidisciplinary, customized, and lifelong treatments are needed to treat PWS. Prader-Willi syndrome (PWS) is a complex genetic disorder caused by lack of expression of paternal genes in the 15q11-q13 region. It leads to hypotonia and feeding challenges infancy, evolving into hyperphagia (insatiable appetite) in childhood, severe obesity, endocrine dysfunctions, and behavioural problems. There is no cure—treatment focuses on symptom management, prevention of complications, and improving quality of life through lifelong multidisciplinary care.

Management:

Importance of Early Diagnosis:

Early diagnosis of PWS allows prompt initiation of nutritional management, growth hormone therapy, endocrine surveillance, and behavioural interventions, which significantly improve growth, body composition, and long-term outcomes. Advances in neonatal

recognition and routine use of methylation testing have improved early detection rates.

- Preventing metabolic disorders and obesity.
- Growth and body composition optimization. ➢ Endocrine deficiency correction.
- Treatment of mental and behavioural issues.
- Enhancement of quality and autonomy in function.
- Growth hormone therapy and organized nutritional control are two therapeutic strategies that can be started quickly with an early diagnosis.
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Pharmacological management:

1. Growth Hormone Therapy:

Recombinant human growth hormone (rhGH) therapy is the most established pharmacological treatment for PWS.

1.1 Advantages:

- Improved linear growth
- Increased lean body mass
- Reduced fat mass
- Improved muscle strength and motor development
- Possible cognitive and behavioral benefits
- GH therapy is recommended in both children and adults with PWS; provided contraindications are excluded.

1.2 Safety and Monitoring

Before initiation, patients should be evaluated for sleep apnea, scoliosis, and glucose intolerance. Regular monitoring during therapy is essential to ensure safety and efficacy.

2. Management of Endocrine Disorders:

- Sex hormone replacement (testosterone in males, estrogen/progesterone in females) for delayed puberty.
- PWS is associated with multiple endocrine abnormalities.

2.1 Hypogonadism:

Sex hormone replacement therapy is often required to induce and maintain puberty, improve bone mineral density, and enhance quality of life. Hypogonadism is common in both males and females with PWS and results in delayed or incomplete puberty, genital hypoplasia, infertility, and low bone mineral density. To initiate and sustain pubertal development, sex hormone replacement treatment is frequently necessary. For men, testosterone is used, and for women, estrogen with or without progesterone is given. Treatment increases quality of life, bone health, muscle mass, and secondary sexual characteristics; dosage should be customized according to age and pubertal stage.

2.2 Hypothyroidism and Adrenal Insufficiency;

Routine screening for thyroid and adrenal dysfunction is recommended, with appropriate hormone replacement when indicated. Hypothyroidism brought on by pituitaryhypothalamic dysfunction. Levothyroxine replacement should be started when a deficiency is found, and routine thyroid function testing is advised, especially infancy and youth. A fraction of patients has also been observed to have central adrenal insufficiency, which increases the likelihood of an adrenal crisis following stress, illness, or surgery. In suspected cases, it is advised to evaluate adrenal function and administer stress-dose corticosteroids during acute illness.

2.3 Diabetes Mellitus;

Obesity-related insulin resistance may lead to type 2 diabetes mellitus, which should be managed according to standard clinical guidelines. The management of diabetes mellitus in individuals with Prader–Willi syndrome (PWS) is centered on intensive weight control, lifestyle modification, and individualized pharmacological therapy. Because obesity and hyperphagia are the main causes of insulin resistance in PWS, dietary therapy with stringent calorie restriction and environmental control of food access is essential. Exercise regimens must be modified to take hypotonia and decrease muscle mass into consideration, but regular, supervised physical activity is advised to increase insulin sensitivity. Because metformin improves insulin sensitivity and has a positive impact on body weight, it is the recommended first-line pharmacological medication. When glycemic control is insufficient, additional oral antidiabetic drugs may be taken however, medicines linked to weight gain or hypoglycemia should be carefully avoided.

3. Management of Hyperphagia and Behavioural symptoms:

There is currently no medication that is uniformly successful for managing hyperphagia in PWS. However, several pharmacological drugs have been studied, including

Agents that alter appetite.

- GLP-1 receptor agonists for controlling blood sugar levels and weight management. Psychotropic drugs for behavioral issues include aggression, anxiety, and obsessiv compulsive symptoms.
- The choice of medication should be customized and closely watched.

Nonpharmacological management:

1. Nutritional management:

Treatment for PWS is based on nutritional intervention.

- Strict calorie-controlled diet to prevent obesity.
- High-protein, low-fat diet.
- Scheduled meals with food access control.
- Regular monitoring of body weight and BMI.

1.1 Infancy

➢ In early life, infants with PWS exhibit hypotonia and poor feeding. Nutritional support, including assisted feeding and high-calorie formulas, may be required to ensure adequate growth.

1.2 Childhood and Adulthood

- As hyperphagia develops, strict dietary supervision becomes essential.
- Low-calorie, well-balanced diets
- Fixed meal timings and portion control
- Restricted access to food
- Continuous caregiver supervision
- Dietary management should be combined with regular physical activity to prevent excessive weight gain.

2. Behavioural and Psychological Interventions:

Behavioural problems are common in PWS and include temper outbursts, compulsive behaviours, and emotional instability. Management strategies include:

- Structured daily routines.

- Consistent behavioural rules.
- Cognitive-behavioural therapy.
- Family and caregiver counselling.
- Early behavioural intervention reduces long-term psychosocial complications.

3. Supportive Therapies:

Supportive care plays a critical role in PWS management:

- Physical therapy: improves muscle tone and mobility.
- Occupational therapy: enhances daily living skills.
- Speech therapy: addresses speech and feeding difficulties.
- Sleep management: treatment of sleep apnea when present.
- Special education programs are beneficial for cognitive and learning difficulties.

4. Multidisciplinary Care:

Optimal management of PWS requires a multidisciplinary team, including:

- Endocrinologists.
- Dietitians.
- Psychologists and psychiatrists.
- Physical and occupational therapists.
- Genetic counselling.
- This integrated approach ensures holistic and lifelong care.

CONCLUSION:

Prader–Willi syndrome is a complex, multisystem genetic disorder resulting from the absence of expression of paternally inherited genes on chromosome 15q11–q13 and is characterized by distinctive, age-dependent clinical manifestations. The condition begins in infancy with severe hypotonia and feeding difficulties and progresses to hyperphagia, obesity, endocrine dysfunction, cognitive impairment, and behavioural disturbances later in life.. Although no curative therapy currently exists, comprehensive multidisciplinary management including growth hormone therapy, strict nutritional supervision, behavioural and psychological support, hormone replacement therapy, and long-term monitoring has significantly improved growth, body composition, functional ability, and quality of life. Early diagnosis and lifelong, coordinated care are essential to prevent complications and reduce disease burden. Continued research into targeted therapies for appetite control, behavioural regulation, and genetic mechanisms is crucial for further improving long-term outcomes and enhancing the overall quality of life of individuals with Prader-Willi syndrome and their families.

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