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UNDERSTANDING PRADER-WILLI SYNDROME: FROM MOLECULAR DIAGNOSIS TO THERAPEUTIC INNOVATIONS

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ABSTRACT

Prader-Willi syndrome (PWS) is a rare, multisystem genetic disorder with an epigenetic basis, caused by a lack of paternal gene expression in the region of chromosome 15q11-q13. Key clinical manifestations include severe hypotonia early in life, hyperphagia leading to obesity, short stature, hypogonadism, cognitive impairment, and multiple endocrine disorders such as growth hormone deficiency, hypothyroidism, and central adrenal insufficiency. Hypothalamic dysfunction plays a central role in the pathogenesis of PWS, responsible for many somatic and behavioral symptoms, including disorders of satiety, temperature regulation, sleep, and emotion. Obesity and its complications - including type 2 diabetes and cardiovascular disease - are a major cause of morbidity and mortality in this group of patients. Molecular diagnosis is mainly based on DNA methylation analysis, which allows detection of all types of genetic alterations in PWS. Currently, there is no causal treatment for the syndrome, and effective management requires a multidisciplinary approach including hormonal treatment, strict dietary control, behavioral interventions, rehabilitation, and possibly pharmacotherapy and new therapeutic options such as GLP-1 agonists, topiramate, oxytocin, naltrexone-bupropion, and matfromin.

KEYWORDS

Prader-Willi Syndrome, PWS, Obesity, GHD, 15q11-Q13, Hyperphagia

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Introduction.

The purpose of this paper is to review current knowledge of the pathophysiology, clinical manifestations, and therapeutic challenges of Prader-Willi syndrome, with a focus on endocrinological and metabolic aspects. Prader-Willi syndrome (PWS) is a rare, multisystem genetic disease that affects the metabolic, endocrine, and nervous systems [1]. The condition was first described in 1956 by Swiss physicians Andrea Prader, Heinrich Willi, and Alexis Labhart, based on observations of nine patients with characteristic clinical features such as short stature, obesity, intellectual disability, and small hands and feet. They were originally identified as Prader-Willi syndrome [2,3]. The disorder most often affects hypothalamic function, resulting in multiple endocrinopathies such as growth hormone deficiency (GHD), hypogonadism, hypothyroidism, central adrenal insufficiency (CAI), and reduced bone mineralization (BMD) [4]. Underlying PWS is a lack of expression of father-derived genes in the 15q11.2-q13 region of chromosome 15 [5], which is regulated by a mechanism in which gene expression depends on its parental origin [6]. In this region, only paternal genes are active, while the maternal allele is silenced by epigenetic mechanisms [5]. Disruption of these genes, involved in RNA processing and neurotransmitter and hormone protein synthesis, among other things, leads to the neurological, hormonal, and metabolic deficits typical of PWS [7]. Three primary genetic mechanisms can lead to the

development of this syndrome. The most common genetic mechanism is a deletion of 5 to 6 Mb, occurring in 65%-75% of individuals with PWS [5,8]. The second most common genetic mechanism is UPD, reported in 20%-30% of individuals [5]. Loss of the maternal 15q11-q13 locus results in a separate syndrome called Angelman syndrome [6,9]. The incidence of PWS is estimated at 1 case per 10,000-20,000 births, with more than 400,000 patients worldwide [10]. The disease affects men and women equally, regardless of race and ethnicity [1]. The vast majority of cases are sporadic, and the risk of having another child in the family remains similar to that of the general population [3]. Although classified as a rare disease, it is one of the more common causes of genetically determined obesity. Approximately 25-30 new cases are diagnosed each year in Poland [3]. The mortality rate in the PWS patient population is about 3% per year [10]. In the past, the acronym HHHO (hypotonia, hypogonadism, hypogonadism, obesity) was used to describe the main clinical features of PWS [3]. The syndrome is characterized by a complex course that includes developmental, metabolic, endocrine, and behavioral changes at different stages of life [11]. Symptoms in early childhood include decreased muscle tone, feeding problems, and slow growth [1,11,12], which can lead to significant developmental delay [8]. Over time, characteristic features of facial dysmorphia, strabismus, and skeletal and muscular deformities appear. Global developmental delay, hyperphagia, and the onset of obesity manifest around age 3 [1]. Mild cognitive impairment and behavioral problems, including self-injury, anxiety, obsessive-compulsive disorder, and outbursts, can occur in childhood along with food seeking, leading to morbid obesity and shortened life expectancy [8,13]. The genetic subtype of PWS can influence the clinical picture, including autistic features and psychiatric disorders [10]. Hypothalamic dysfunction causes growth hormone deficiency, hypogonadism, and dysregulation of energy balance associated with hypoactivity and insatiable hunger, resulting in increased body fat and decreased muscle mass [2]. Hunger mechanisms in PWS patients are pathologically activated, which is associated with a lack of satiety and impaired reward control in the brain [14]. Prader-Willi syndrome is the most common genetic cause of severe life-threatening obesity [10]. In children and adolescents, overweight and obesity occur in about 40% of patients, while in adulthood, this percentage increases to 80-90% [15]. Unlike in other genetic syndromes, hyperphagia in PWS does not appear from birth, but usually after the age of three and continues throughout life [8]. Due to the numerous complications of obesity, including cardiovascular disease, diabetes, hypertension, sleep apnea, gastric distension, and necrosis, early diagnosis and weight control are crucial [7,16,17]. Patients are also at risk for orthopedic disorders, sleep problems, and other hormonal complications [18]. Despite the development of clinical care, the life expectancy of patients with PWS is only about 29.5 years [6]. The main causes of death are respiratory failure, circulatory failure, gastrointestinal disorders, and infections [8]. Delay in diagnosis is associated with additional costs, stress for families, and loss of valuable time to initiate treatment [7]. Among the greatest difficulties are appetite changes ranging from anorexia to the development of hyperphagia, persistent hypotonia and low muscle mass, and difficult-to-control behaviors such as obsessiveness, rigid routines, and angry outbursts [18]. Despite advances in knowledge of the syndrome's genetics and phenotypes, the mechanisms responsible for hyperphagia and obesity remain incompletely elucidated [19]. Management of the condition involves a strict diet, regular physical activity, and control of eating behavior, which poses a major challenge for families and caregivers [18]. According to a 2014 survey, the most important unmet needs for people with PWS are reduced cravings and improved eating behavior [8]. Although there is currently a lack of approved medications for the treatment of hyperphagia in PWS, studies are underway on various substances such as metformin, topiramate, liraglutide, and oxytocin. However, they are still limited, and there are no widely accepted consensus guidelines for these drugs in children with PWS [15,18]. In clinical practice, weight management in patients with PWS is mainly achieved through diet and exercise with strict food restriction [17,20]. The standard of care for children with PWS is growth hormone (GH) therapy, which has beneficial effects on body composition, psychomotor development, and growth [7,18]. Only comprehensive, multidisciplinary care offers a chance to improve patients' quality of life and achieve a life expectancy similar to that of the population [3]. Obesity prevention - through GH therapy and lifestyle changes implemented from childhood - is a key component of treatment [15]. Although bariatric surgery is an effective method of weight reduction, its use in PWS patients is still controversial [21]. This review summarizes the genetics, clinical manifestations, diagnosis, and treatment of PWS, with a focus on endocrine and metabolic aspects.

Materials and Methods

A comprehensive review of articles published in scientific journals was conducted using online research platforms such as PubMed and Google Scholar. Articles were identified using the following search terms: "Prader-Willi syndrome," "PWS," "obesity," "GHD," „15q11-q13," and „hyperphagia".

Genetics

Prader-Willi syndrome (PWS) is a complex genetic disorder caused by the inactivation of father-derived genes within the region of chromosome 15q11.2-q13 [1,10]. This region contains numerous genes subject to an imprinting mechanism in which only the paternal copy is expressed, while the one inherited from the mother remains inactive due to epigenetic processes [12,21]. The epigenetic process is reversible and occurs during both male and female gametogenesis. Epigenetics, which plays a key role in regulating gene expression, works by, among other things, methylating DNA at specific sequences, such as cytosines, which affects the "on" or "off" of specific genes. Approximately 150 genes in humans are known to undergo imprinting and contain CpG-rich regions characterized by differential methylation depending on the origin of the allele [9]. The vast majority of PWS patients lack about 20 paternal genes, including NDN, MKRN3, MAGEL2, SNURF, SNRPN, SNORD116, SNORD115, or SNHG14 (formerly UBE3A-ATS) [13]. The MAGEL2 gene, highly expressed in the hypothalamus, is associated with autism spectrum disorders. MKRN3, on the other hand, is involved in hormonal regulation and control of sexual maturation. Loss of function of the SNRPN gene, which encodes a ribonucleoprotein and SNURF polypeptide, leads to abnormalities in nervous system development and endocrine function [3]. If, on the other hand, the deletion occurs in an analogous region of chromosome 15 inherited from the mother, it leads to the development of Angelman syndrome [3,9]. PWS was the first disease for which an association with imprinting - a mechanism in which gene expression depends on the parent from which the gene is derived - was confirmed [1]. Lack of paternal gene activity in the 15q11-q13 region results in the development of the typical clinical picture of PWS [12]. Most cases of PWS occur sporadically [19]. Loss of function of this region can have three primary causes: deletion is the most common (about 70% of cases), maternal uniparental disomy of chromosome 15 (matUPD - about 25%) is observed less frequently, and the least common is a defect in the imprinting mechanism (less than 5%), in which the paternal copy acts like the maternal one [8,13]. No single gene mutation is responsible for the full picture of PWS, confirming that the disease results from loss of function of several neighboring genes, i.e., it represents the so-called adjacent gene syndrome [13]. Individuals with maternal UPD who inherit both copies of chromosome 15 from their mother may develop other recessive diseases if the mother carries the relevant mutations. Chromosome 15 contains numerous recessive genes associated with various disorders, such as hearing loss, heart disease, epilepsy, and metabolic defects [10]. Deletions are divided into two main subtypes based on their size: Type I (about 6 Mb) and Type II (500 kb smaller). Type I includes an additional four genes: NIPA1, NIPA2, CYFIP1, and GCP5 [5]. NIPA genes encode magnesium ion transporters and are important for normal brain function, muscle function, and metabolic processes related to insulin and glucose. Lower magnesium levels have been observed in people with type I deletion. The GCP5 gene, on the other hand, has been linked to ADHD and compulsive behavior, more often seen specifically in patients with this type of deletion [22]. Type I is also associated with a more severe clinical picture than type II. Atypical deletions, larger or smaller than classic types, occur in 7-9% of patients [5]. The smallest lesions in the 15q11-q13 region involve microdeletions of genes encoding snoRNA-type noncoding RNAs, such as SNORD115 and SNORD116. Studies in mice with abnormal transcripts of SNORD116 counterparts confirm the presence of typical symptoms of PWS, such as hyperphagia and stunted growth [9]. Individuals with maternal disomy (UPD), who have no paternal copy of chromosome 15, tend to exhibit fewer characteristic physical features than those with deletions. Nevertheless, they are more prone to psychosis and autistic symptoms [9,19]. On the other hand, individuals with deletions - especially type I - are more likely to have a more severe phenotype, higher body mass index, scoliosis, and more severe behavioral difficulties [19].

Symptoms

The symptoms of Prader-Willi syndrome (PWS) vary depending on the age of the patient, with marked differences in clinical expression at different stages of life. The syndrome is historically divided into two stages: the first is developmental delay, and the second is the onset of hyperphagia and obesity [5,10]. Prenatal features of PWS include reduced fetal activity (in 88% of cases), low body weight relative to gestational age (65%), and a larger head-to-abdomen circumference ratio (43%). Polyhydrosis is present in 34% of cases, which may suggest difficulty in sucking and swallowing [5,12]. In addition, early or late deliveries are more

common in pregnancies with maternal dysmorphia [10]. Prenatal hypotonia leads to decreased fetal movement, abnormal fetal position during delivery, and a higher number of assisted deliveries or cesarean sections [21]. The height and weight of newborns with PWS are 15-20% less than that of healthy children [1]. In infancy, PWS manifests as hypotonia, feeding difficulties, poor suckling reflex, and low muscle mass and strength [10]. Underdevelopment during this period can lead to developmental delay, temperature instability, hypopigmentation, hypogonadism (e.g., micropenis and cryptorchidism in boys), as well as short stature and small hands and feet [1]. Early childhood (2-6 years) is characterized by the onset of hyperphagia, which leads to obesity if not properly controlled [10]. In addition, children with PWS may exhibit abnormal body composition, decreased muscle mass, increased body fat, and behavioral disorders such as hiding food, taking food out of the trash can, stealing food, rage attacks, stubbornness, obsessive disorders, and affective disorders [5,16]. Because of hypothalamic-pituitary axis dysfunction, patients with PWS should also be evaluated for central hypothyroidism and adrenal insufficiency [16].

Hypotonia

Hypotonia is a hallmark symptom in infants with PWS, leading to feeding difficulties, poor weight gain in early life, and the need for specialized feeding devices [1]. Early diagnosis is important, as molecular testing should be performed whenever hypotonia is observed in infants [1,13].

Dysmorphic features

People with PWS in infancy have distinctive facial features such as almond-shaped eyes, narrow nasal bridge, high forehead, thin upper lip, and enamel hypoplasia. In addition, small hands and feet may be present [1,13]. Hypopigmentation of the skin, hair, and eyes is also common, especially in individuals with deletion of the OCA2 gene [21].

Behavioral and psychiatric disorders

PWS is associated with several personality traits and specific behaviors. Infants and young children are typically described as cheerful, submissive, and cooperative. Early childhood is characterized by tantrums, stubbornness, and controlling and manipulative behavior. In adolescence, affected individuals are characterized as cognitively and behaviorally inflexible, ritualistic, prone to sudden and intense emotional and behavioral dysregulation with frequent sensory/self-injurious activity [19]. Increased behavioral and emotional problems with age can affect quality of life, especially in adulthood, although early diagnosis can improve prognosis [22]. Autism-like features and the occurrence of psychosis in 10-20% of patients in young adulthood are also noted among PWS [13,21].

Developmental delay

Delayed motor development occurs in 90-100% of children with PWS, with average early milestones reached at about twice the normal age [21]. The average age of independent walking is about 27 months [1]. Intellectual disability is generally apparent by the time a child reaches school age. Tests indicate that most people with PWS fall within the range of mild intellectual disability (mean intelligence quotient [IQ]: 60-70 [21]. Regardless of IQ scores, most children have severe learning difficulties [21].

Hypogonadism

Hypogonadism, or insufficient production of sex hormones, is common in people with PWS. It can result from primary gonadal insufficiency or disorders of the hypothalamic-pituitary axis [8]. The etiology of hypogonadism in PWS is quite heterogeneous and may be due to a defect in the hypothalamic-pituitary axis, a failure of the gonadal response, or a combination of the two[5,13]. Boys may have micropenis, cryptorchidism and small testicular volume, and girls may have genital hypoplasia [1,23]. At birth, the incidence of cryptorchidism and scrotal hypoplasia ranges from 75% to 95%. Micropenis or a small penis occurs in males at a frequency of 78% to 90% [2]. Most studies report normal penile length at birth and in early childhood. However, over time, penis length begins to drop below -2SD compared to healthy men. The smaller penile size, combined with the large suprapubic fat pad observed in many obese PWS patients, can lead to difficulty urinating [4]. Pubertal arrest is seen at Tanner's stage 3 in the evaluation of sexual maturity, characterized by testicular failure and small testicular size that persists into adulthood [1]. Testicular size can develop to a volume of 6-7 milliliters and remain small into adulthood [4]. Women with Prader-Willi syndrome are born with hypoplasia of the external genitalia [1]. In girls, the respective rates of hypoplasia of the clitoris

and labia minora are 93% and 88% [2]. Puberty usually begins at a typical age, but the progression of breast tissue to Tanner 3 and 4 is usually significantly delayed, with very few patients achieving Tanner 5 breast development [1,4]. Spontaneous menarche is rare [1]. The average age of first menstruation is about 20 years [4]. Both men and women with Prader-Willi syndrome are considered infertile [1]. Spontaneous pregnancies are possible in some women with PWS, but the risk of Angelman syndrome in the offspring is high [5]. An increased risk of early adrenarche (14-30%) also occurs in patients with PWS [4].

Growth hormone deficiency

Low growth is one of the key symptoms of Prader-Willi syndrome (PWS) and is directly related to abnormalities in the GH-IGF-1 axis. Growth hormone deficiency (GHD) in PWS occurs in a significant proportion of patients, with a frequency varying between 40% and 100%, and alteration of this axis is considered a hallmark of the syndrome. In patients with PWS, GHD occurs in about 74% of cases, and IGF-1 deficiency is present in almost all (almost 100%) of patients [4]. Changes in the central growth system begin as early as the prenatal period, when infants with PWS are on average 15-20% smaller than their siblings. Growth deficiency is evident as early as childhood, and the lack of a growth spurt during adolescence results in an average height of 155 cm in males and 148 cm in females if no treatment is undertaken [13]. GH deficiency also affects metabolism, leading to increased fat mass and muscle weakness, which promotes obesity. In addition, deficiency of the hormone causes lipid disorders such as elevated total and LDL cholesterol, which in turn increases the risk of cardiovascular disease [3]. Studies have shown that 63-74% of PWS patients have morphological changes in the pituitary gland on MRI scans, although this does not always correlate with pituitary hormone deficiencies [4].

Central adrenal insufficiency

Central adrenal insufficiency (CAI) is another disorder that can occur in PWS patients. Reduced cortisol levels lead to disruptions in carbohydrate, fat, and protein metabolism [6]. Symptoms of this insufficiency can include reduced weight gain, prolonged jaundice in newborns, weakness, recurrent infections, headaches, and muscle and joint pain in older children. In cases of partial glucocorticoid deficiency, symptoms may be subtle and only manifest in stressful situations, making diagnosis and treatment difficult [24].

Central hypothyroidism

Central hypothyroidism occurs in patients with PWS, with a frequency of 2% to 30% [5]. In adult patients, the prevalence of hypothyroidism is similar to the general population [3]. If this condition is suspected, it is necessary to monitor thyroid function, especially before and during growth hormone (rhGH) therapy [5]. Test results such as TSH levels > 10 mIU/L and low T4 levels indicate primary hypothyroidism, while low TSH levels combined with decreased T4 may suggest central hypothyroidism [5].

Other symptoms

Skeletal changes are also an important symptom in PWS. An increased incidence of osteoporosis and fractures affects about 29% of adult patients with PWS [5]. Because of the risk of scoliosis, radiologic examinations are recommended for early detection of this deformity, starting around 18 months of age [12]. Other symptoms of the syndrome include sleep disturbances, epilepsy, body temperature instability, and hypopigmentation of the skin, irises, and hair, which affects 30-50% of patients [1]. Temperature instability, characterized by lower body temperature, is common, and fever may be absent even in cases of severe infection [24]. In addition, hypothalamic dysfunction can lead to problems with the vomiting reflex and frequent urination at night [3].

Hyperphagia and obesity

Prader-Willi syndrome (PWS) has historically been described in two clinical stages [10]. The first stage involves infancy, in which patients have feeding problems, muscle hypotonia, and abnormal weight gain, and the second stage involves childhood, when hyperphagia leading to obesity becomes the main feature [18]. However, modern classifications, based on new research, propose a more complex division [10,12]. Patients with PWS go through seven dietary stages, which are related to appetite and weight gain [13,19]. Stage 0, which occurs prenatally, is characterized by reduced fetal activity and stunted growth compared to siblings [21]. Early infancy (phase 1a) is associated with hypotonia, feeding difficulties, and decreased appetite (0-9 months), while in phase 1b (9-24 months), appetite, food intake, and weight gain return to normal. From the

age of two (phase 2a), children begin to gain weight, but appetite remains unchanged, and in phase 2b (4.5-8 years), there is an increased interest in food, leading to excessive weight gain due to a marked increase in appetite [18]. Hyperphagia and obesity become more pronounced during school age (mean age of onset: 8 years), and become the dominant symptoms in childhood (phase 3) and adulthood (phase 4) [10,15]. The last phase, phase 4, occurs in adulthood. In this phase, appetite is no longer insatiable [13]. Weight gain in PWS patients begins between 18 and 36 months of age, but this is not associated with a significant increase in food intake. Children with PWS require 20-30% less energy than healthy children of the same age [5]. Central obesity, a characteristic of PWS, leads to numerous complications, increasing morbidity and mortality [1,13]. In adult patients, hyperphagia can lead to choking, and eating behaviors include overeating and consumption of inedible substances [1]. The prevalence of obesity in PWS varies by age, reaching 40% in children and 82% to 98% in adults [25]. The biological mechanisms of impaired satiety in PWS are still incompletely understood, but potential causes include alterations in the satiety control center, dysregulation of hormones affecting appetite, and reduced metabolic rate, leading to energy imbalance. Additional factors include weakened muscle tone and a higher percentage of body fat [5]. Sleep disturbances, including decreased REM sleep and sleep apnea, also increase the risk of developing severe obesity [18]. Disruption of hypothalamic pathways responsible for controlling satiety results in a persistent, insatiable appetite and an excessive desire to eat [15]. Functional magnetic resonance imaging has shown higher activity in brain areas responsible for reward (e.g., nucleus accumbens, amygdala) and lower activity in the hypothalamus and hippocampus in response to eating in PWS subjects compared to non-PWS obese subjects [15]. Higher levels of ghrelin, an orexigenic hormone that stimulates appetite and GH secretion, have also been observed in PWS subjects, and its levels are elevated in children with PWS, which may contribute to the development of hyperphagia and obesity [5,15]. Several orexigenic and anorexigenic hormones are thought to be involved in the development and maintenance of obesity in PWS, through appetite dysregulation [15].

Ghrelin: a potent orexigenic hormone, synthesized mainly in the fundus of the stomach during fasting and starvation, and its levels are suppressed by food intake [5,15]. Ghrelin increases appetite through central regulatory mechanisms in the hypothalamus, stimulates GH secretion, regulates energy homeostasis and brown fat thermogenesis, and stimulates gastric emptying [15]. The number of cells expressing ghrelin in PWS patients was 2 to 3 times higher than in controls. Ghrelin is elevated in children with PWS, precedes the onset of obesity, and is involved in the onset of the hyperphagic stage [5]. In addition, ghrelin levels remained elevated and were not adequately suppressed after eating in PWS subjects [15].

Leptin is a peptide produced by adipose tissue and is involved in the regulation of appetite and fat storage. Released by adipocytes in response to satiety signals, it reduces food intake and energy metabolism by inhibiting neuropeptide Y (NPY) neurons in the arcuate nucleus [15].

TRH-TSH: Changes in this axis result in decreased energy expenditure [5].

GH: Deficiency leads to decreased muscle mass and increased body fat [5].

Obestatin: produced in the stomach by post-translational modifications of ghrelin. Unlike ghrelin, obestatin inhibits food intake, suppresses gastric emptying, and reduces weight gain. A significant difference in plasma obestatin levels was observed between obese PWS and non-PWS obese patients [5].

Failure to adequately control access to food during childhood, without dietary and behavioral interventions, leads to the development of severe obesity [25]. Type 2 diabetes mellitus (T2DM) is a common obesity-related complication in PWS, and without appropriate treatment can occur as early as a young age, around 20 years old [11,26]. Overweight-related complications are the leading cause of death in PWS patients, including obstructive sleep apnea syndrome, type 2 diabetes, steatohepatitis, cardiopulmonary failure, and thromboembolic disease [3,25].

Morbidity and mortality

The prognosis of patients with PWS depends on the time of diagnosis and the extent of complications. Early initiation of treatment and prevention of obesity increases the chances of achieving life expectancy. Complications such as obesity, diabetes, and heart failure significantly reduce life expectancy [10,22]. Mortality in PWS is estimated at 3% per year. The most common causes of death are respiratory failure (31%),

heart failure (16%), gastrointestinal disorders (10%), and infections (9%). Choking (6%) and accidents (6%) were reported more frequently in childhood or as young adults [22]. After a growth spurt, the most common causes of death are cardiovascular disease, obstructive sleep apnea, diabetes, adrenal insufficiency, and gastric perforation due to uncontrolled consumption of large amounts of food [3]. The life expectancy of people with PWS is 29.5 years [6,22]. The higher prevalence of central adrenal insufficiency (CAI) may explain the sudden deaths in patients with PWS [21].

Diagnosis

Due to the rarity of Prader-Willi syndrome (PWS) and the variable severity of clinical symptoms, diagnosis of the condition early in life is sometimes difficult. Diagnosis is largely based on observation of clinical symptoms. To facilitate diagnosis, the Holm Diagnostic Scale, published in 1993, was developed, which classifies symptoms as major (1 point each), secondary (0.5 points each), and ancillary, which are not scored [3]. A score of at least 5 points, including at least 4 for the main symptoms, is required for a diagnosis of PWS in children under 3 years of age. In older patients (older than age 3), the diagnosis requires a minimum of 8 points, of which at least 5 must be major criteria [3]. Main symptoms include muscle hypotonia and feeding difficulties in infancy, delayed weight gain in the first year of life, satiety disturbances and excessive appetite that appear after the second year of life, rapid weight gain leading to obesity, characteristic facial features (e.g. including a narrow face, almond-shaped eyelid crevices, thin upper lip), hypogonadism, and delayed psychomotor development and the presence of cytogenetic changes in the 15q11-q13 region [3,12]. Secondary symptoms include, but are not limited to: reduced prenatal and neonatal motility, quiet crying, behavioral abnormalities (e.g., impulsivity, stubbornness, aggression, tendency to steal), sleep problems, short stature, hypopigmentation, small hands (< 25th percentile for age) and feet (< 10th percentile for age), thick saliva, and articulatory difficulties and ocular disorders (strabismus, myopia) [3,12]. Ancillary criteria include thermoregulatory abnormalities, decreased pain threshold, infrequent vomiting, spinal deformities (scoliosis, kyphosis), early adrenarche, osteoporosis, specific abilities (e.g., puzzle-solving), and normal electromyography (EMG) [3,12]. Definitive confirmation of the diagnosis of PWS requires genetic testing. Among the most commonly used methods are fluorescence in situ hybridization (FISH), DNA methylation analysis, and DNA sequencing [3]. Molecular testing is essential to confirm the diagnosis, especially in cases where the clinical picture suggests PWS. The indications for genetic testing vary depending on the age of the patient. In infants up to age 2, the main indication is hypotonia and poor suckling. In the 2-6 age group, psychomotor development delay and a history of hypotonia are important. In children between 6 and 12 years of age, a history of hypotonia, excessive eating, and central obesity should be noted. In adolescents and adults, on the other hand, intellectual disability, unrestrained appetite, hypogonadism, and adaptive and behavioral difficulties are characteristic [10,12,21]. The most effective method for detecting PWS is DNA methylation analysis - techniques such as Southern blot or methylation-specific PCR detect PWS in 99% of cases, regardless of the genetic cause (paternal deletion, maternal disomy, or imprinting defect). In healthy individuals, two alleles of the SNRPN gene are present (one methylated, one unmethylated), while PWS patients have only the methylated maternal allele [13]. FISH can detect 15q11-q13 deletions, while the use of chromosome microarrays can identify cases of maternal disomy [1,6,7].

Treatment

Prader-Willi syndrome (PWS) remains a condition with no causal treatment options, necessitating a focus on symptom control, preventing complications, and improving patients' well-being [5]. Comprehensive care is required, which should include growth hormone (rhGH) therapy, appropriate diet, regular physical activity, rehabilitation, as well as support from a psychologist and speech therapist. Obesity, which is the predominant symptom of PWS, contributes to components of the metabolic syndrome, such as hypertension, lipid disorders, and insulin resistance, leading to a shorter life expectancy. Therefore, prevention and treatment of obesity is an overarching goal of care for patients with PWS [5]. Therapeutic management depends on the age of the patient. In infants, hypotonia, feeding difficulties, and abnormal weight gain are observed, which may require consultation with the nutrition team and the introduction of high-calorie formulas or special feeding techniques [1,18]. During this period, the goal is to achieve normal growth without excessive weight gain, maintaining the child's weight between the 50th and 75th percentile [15]. If necessary, specialized pacifiers or nasogastric/gastrostomy probes are used to ensure adequate nutrient delivery [10]. Between the ages of 2 and 4, weight gain occurs without increasing the caloric content of the diet, so early implementation of nutritional counseling and caregiver education is important [4]. The diet should be low in calories (70-80%

of the age and gender norm), with a low glycemic index, with a macronutrient breakdown: 45% carbohydrate, 30% fat, 25% protein, and a fiber intake of more than 20 grams per day [5,21]. Energy requirements of people with PWS rarely exceed 1,000-1200 Kcal/day [21]. Frequent, small meals are recommended to reduce hyperphagia and compulsive behavior toward food [25]. Due to increased appetite, physical restraints such as locking refrigerators and cabinets are often necessary [13]. Hyperphagia also increases the risk of choking due to rapid swallowing of food [1]. Monitoring body weight and diet composition is essential in the prevention of diabetes and other metabolic complications associated with obesity [13]. Exercise, especially strength training, is important at every stage of life - it improves resting metabolism and counteracts obesity, as well as promoting motor development and distracting from food [3,15]. In cases where conservative treatment is unsuccessful (often due to lack of adherence), pharmacotherapy is considered [3]. Growth hormone therapy, approved by the FDA in 1985, remains the most widely used and best studied intervention in patients with PWS [27]. Treatment with rhGH leads to improvements in height, body composition, bone mineralization, and motor and cognitive development [13,19]. In adults, continuing or initiating GHT provides benefits for body composition, physical performance, and quality of life [19]. Treatment should begin by age 2 at the latest, as early treatment has shown benefits in head circumference, motor and language development, and cognitive function [13]. Studies have shown that children treated with rhGH have lower body fat, higher muscle mass, and a better lipid profile than those not treated [16]. GH therapy has a beneficial effect on HDL levels and a reduction in LDL, triglycerides, and total cholesterol [3]. However, there are contraindications to its use, such as severe obesity, untreated sleep apnea, active cancer, or psychosis [3]. Children with PWS are at increased risk of obstructive and central apnea, and this risk may increase with GH treatment, possibly due to lymphatic proliferation. Because of the risk of obstructive sleep apnea, a sleep study is recommended before and after starting therapy, as well as annual follow-ups. Scoliosis, hypothyroidism, and IGF-1 should also be monitored [13]. Despite these potential negative effects, the long-term benefits of GHT are still considered to outweigh the potential risks [6]. Dosing of rhGH should be individually adjusted, and the initial dose in children is 0.18-0.3 mg/kg/week as daily subcutaneous injections with careful monitoring of clinical status, bone age, and serum IGF-1 levels at regular intervals [9]. Increased IGF-1 levels, as well as increased IGF-1/insulin-like growth factor-binding protein-3 (IGF-BP3) ratios, increase the risk of side effects, especially increased sleep apnea, and carry the risk of developing or recurring previously treated cancer. Without GH treatment, about 80% of patients die between the ages of 11 and 40; therapy significantly reduces the mortality rate from 3% to 1.25% per year [3]. In Poland, reimbursement of therapy for children was introduced in 2006, and in 2016 it was extended to adult patients continuing treatment after age 18. In adults, a dose reduction to 30-50% of the pediatric dose is recommended. The main goal of adult treatment, as in the pediatric population, is to prevent obesity and its complications, which contribute to increased patient mortality[3]. Non-registered indications such as topiramate, metformin, naltrexone-bupropion, and GLP-1 agonists (e.g., liraglutide), which affect appetite and metabolism, are also being used in the treatment of obesity on a trial basis [4,18].Topiramate is an anti-obesity drug used off-label for weight loss. Its mechanism is not fully understood. Topiramate appears to block sodium and calcium channels, increasing the suppressive effect of GABA. Metformin is an oral drug classically used in type 2 diabetes to improve hyperglycemia, and is also used off-label to treat obesity and pre-diabetes.In a pilot study, it was used in a group of 21 children and adolescents with Prader-Willi syndrome who had insulin resistance and impaired glucose tolerance. The therapy yielded positive results in terms of reducing food-related anxiety, assessed by a special hyperphagia questionnaire, although no weight loss was observed. Naltrexone-bupropion is a combination drug used to treat obesity and impulsive behavior. Naltrexone is an opioid receptor antagonist, and bupropion is a dopamine and norepinephrine reuptake inhibitor. The FDA has approved this drug for the treatment of obesity [18]. Glucagon-like peptide 1 (GLP-1) receptor agonists are hormones produced by L-cells located in the ileum and colon that promote insulin secretion, reduce glucagon production, and lower plasma ghrelin levels [8,18]. Recent studies suggest that the use of GLP-1 agonists, such as exenatide and liraglutide, is beneficial in adult patients with PWS and type 2 diabetes, promoting weight loss, increasing satiety, and improving blood glucose control [4]. A systematic review found that patients with PWS have reduced gastrointestinal motility and increased feelings of fullness after meals. Liraglutide, which has a short-term effect and is administered daily, is approved by the FDA and EMA for the treatment of obesity in people over 12 years of age [18]. Oxytocin is a neuropeptide that has a wide range of indications. It induces weight reduction by increasing lipolysis, as well as decreasing appetite, which can lead to reduced food intake. Five studies have examined the effects of administering an intranasal oxytocin analog (carbetocin) in children with PWS [18]. Preliminary results indicate their beneficial effects on weight loss and improved social behavior with good treatment tolerance and no significant side effects [3].

Given the lack of approved therapies that effectively control hyperphagia in Prader-Willi syndrome, and its key role in the development of morbid obesity and metabolic complications, there is an urgent need for further research and development of new targeted drugs that modulate appetite and central regulation of hunger and satiety. Surgical treatment of obesity remains controversial due to its ineffectiveness against central hyperphagia and the risk of complications. In addition, gastric restriction surgeries, such as bands or balloons, may increase the risk because, again, hyperphagia remains unaltered, and restriction procedures may predispose to gastric distension and necrosis [19]. Cryptorchidism is observed in most young boys with Prader-Willi syndrome. While treatment with human chorionic gonadotropin may be effective in some cases, most require orchiopexy, preferably before the age of one [1,3]. Hormonal treatment (testosterone, estrogen) must be administered with caution, taking into account the risk of side effects, such as aggression in boys and osteoporosis in girls [6]. Testosterone treatment in male patients is usually started with 50 mg intramuscularly every 4 weeks (about 33-50% of the recommended dose for adult men with hypogonadism). This dose is gradually increased under the control of clinical symptoms and serum testosterone levels [3]. Women without contraindications can be treated with a low-dose estrogen patch; progesterone can be added after the onset of menstruation [28,29]. The care of patients with PWS should also include ongoing psychological support, occupational therapy, and education tailored to cognitive needs. In some cases, it is necessary to implement psychiatric pharmacotherapy [3,30]. Medications used occasionally to treat behavioral problems include stimulants, alpha-adrenergic agonists, beta-blockers, mood stabilizers (lithium, valproate, lamotrigine), and typical and atypical antipsychotics and antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) [10].

Conclusions

Prader-Willi syndrome (PWS) is a rare, genetic disorder with a complex and multisystem pathogenesis that includes, among other things, disorders of the hypothalamic-pituitary axis, leading to multiple endocrinopathies and characteristic behavioral and metabolic features, with hyperphagia and obesity at the forefront. Early diagnosis and multispecialty care are key to improving patients' quality of life and long-term prognosis. A comprehensive approach, including hormonal treatment (especially rhGH), appropriate diet therapy, regular physical activity, and psychological support, is particularly important. Currently, only growth hormone is an approved drug therapy with proven efficacy in the treatment of PWS symptoms, especially in the context of body composition, lipid profile, and cognitive function. However, a key and still unmet area remains the treatment of hyperphagia - a symptom with a huge impact on patients' daily functioning and mortality. Several potential drug therapies are currently under investigation, such as GLP-1 receptor agonists (liraglutide, semaglutide), oxytocin, topiramate, metformin, or combination formulations such as naltrexone-bupropion. Preliminary results suggest some efficacy in reducing appetite, improving satiety, and reducing weight and impulsive behavior. Nevertheless, further clinical studies are needed. In light of current data, it is necessary to continue research on new appetite-modulating drugs and to integrate the care of PWS patients within specialized multidisciplinary centers.

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REFERENCES

1. Fermin Gutierrez, M. A., Daley, S. F., & Mendez, M. D. (2024). Prader-Willi Syndrome. In *StatPearls*. StatPearls Publishing.
2. Noordam, C., Höybye, C., & Eiholzer, U. (2021). Prader-Willi syndrome and hypogonadism: A review article. *International Journal of Molecular Sciences, 22*(5), 2705. https://doi.org/10.3390/ijms22052705
3. Drabik, M., Lewiński, A., & Stawerska, R. (2022). Management of Prader-Labhart-Willi syndrome in children and in adults, with particular emphasis on the treatment with recombinant human growth hormone. *Pediatric Endocrinology, Diabetes and Metabolism, 28*(1), 64–74. https://doi.org/10.5114/pedm.2022.112861
4. Heksch, R., Kamboj, M., Anglin, K., & Obrynba, K. (2017). Review of Prader-Willi syndrome: The endocrine approach. *Translational Pediatrics, 6*(4), 274–285. https://doi.org/10.21037/tp.2017.09.04
5. Alves, C., & Franco, R. R. (2020). Prader-Willi syndrome: Endocrine manifestations and management. *Archives of Endocrinology and Metabolism, 64*(3), 223–234. https://doi.org/10.20945/2359-3997000000248
6. Chung, M. S., Langouët, M., Chamberlain, S. J., & Carmichael, G. G. (2020). Prader-Willi syndrome: Reflections on seminal studies and future therapies. *Open Biology, 10*(9), 200195. https://doi.org/10.1098/rsob.200195
7. Kimonis, V. E., Tamura, R., Gold, J. A., et al. (2019). Early diagnosis in Prader-Willi syndrome reduces obesity and associated co-morbidities. *Genes, 10*(11), 898. https://doi.org/10.3390/genes10110898
8. Mahmoud, R., Kimonis, V., & Butler, M. G. (2023). Clinical trials in Prader-Willi syndrome: A review. *International Journal of Molecular Sciences, 24*(3), 2150. https://doi.org/10.3390/ijms24032150
9. Angulo, M. A., Butler, M. G., & Cataletto, M. E. (2015). Prader-Willi syndrome: A review of clinical, genetic, and endocrine findings. *Journal of Endocrinological Investigation, 38*(12), 1249–1263. https://doi.org/10.1007/s40618-015-0312-9
10. Butler, M. G., Manzardo, A. M., & Forster, J. L. (2016). Prader-Willi syndrome: Clinical genetics and diagnostic aspects with treatment approaches. *Current Pediatric Reviews, 12*(2), 136–166. https://doi.org/10.2174/1573396312666151123115250
11. Höybye, C., & Tauber, M. (2022). Approach to the patient with Prader-Willi syndrome. *Journal of Clinical Endocrinology & Metabolism, 107*(6), 1698–1705. https://doi.org/10.1210/clinem/dgac082
12. Butler, M. G., Miller, J. L., & Forster, J. L. (2019). Prader-Willi syndrome—clinical genetics, diagnosis and treatment approaches: An update. *Current Pediatric Reviews, 15*(4), 207–244. https://doi.org/10.2174/1573396315666190716120925
13. Kalsner, L., & Chamberlain, S. J. (2015). Prader-Willi, Angelman, and 15q11-q13 duplication syndromes. *Pediatric Clinics of North America, 62*(3), 587–606. https://doi.org/10.1016/j.pcl.2015.03.004
14. Holland, A., Manning, K., & Whittington, J. (2022). The paradox of Prader-Willi syndrome revisited: Making sense of the phenotype. *EBioMedicine, 78*, 103952. https://doi.org/10.1016/j.ebiom.2022.103952
15. Muscogiuri, G., Barrea, L., Faggiano, F., et al. (2021). Obesity in Prader-Willi syndrome: Physiopathological mechanisms, nutritional and pharmacological approaches. *Journal of Endocrinological Investigation, 44*(10), 2057–2070. https://doi.org/10.1007/s40618-021-01574-9
16. Aycan, Z., & Baş, V. N. (2014). Prader-Willi syndrome and growth hormone deficiency. *Journal of Clinical Research in Pediatric Endocrinology, 6*(2), 62–67. https://doi.org/10.4274/jcrpe.1228
17. Diene, G., Angulo, M., Hale, P. M., et al. (2022). Liraglutide for weight management in children and adolescents with Prader-Willi syndrome and obesity. *Journal of Clinical Endocrinology & Metabolism, 108*(1), 4–12. https://doi.org/10.1210/clinem/dgac549
18. Erhardt, É., & Molnár, D. (2022). Prader-Willi syndrome: Possibilities of weight gain prevention and treatment. *Nutrients, 14*(9), 1950.
19. Whitman, B. Y. (2024). Prader-Willi syndrome: The more we know, the less we know. *Missouri Medicine, 121*(3), 235–241.
20. Nolan, B. J., Proietto, J., & Sumithran, P. (2022). Intensive management of obesity in people with Prader-Willi syndrome. *Endocrine, 77*(1), 57–62. https://doi.org/10.1007/s12020-022-03064-1
21. Cassidy, S. B., Schwartz, S., Miller, J. L., & Driscoll, D. J. (2012). Prader-Willi syndrome. *Genetics in Medicine, 14*(1), 10–26. https://doi.org/10.1038/gim.0b013e31822bead0
22. Butler, M. G. (2023). Prader-Willi syndrome and chromosome 15q11.2 BP1-BP2 region: A review. *International Journal of Molecular Sciences, 24*(5), 4271. https://doi.org/10.3390/ijms24054271
23. Noordam C, Höybye C, Eiholzer U. Prader-Willi Syndrome and Hypogonadism: A Review Article. *Int J Mol Sci*. 2021;22(5):2705. Published 2021 Mar 8. doi:10.3390/ijms22052705
24. Kusz, M. J., & Gawlik, A. M. (2022). Adrenal insufficiency in patients with Prader-Willi syndrome. *Frontiers in Endocrinology, 13*, 1021704. https://doi.org/10.3389/fendo.2022.1021704
25. Barrea, L., Vetrani, C., Fintini, D., et al. (2022). Prader-Willi syndrome in adults: An update on nutritional treatment and pharmacological approach. *Current Obesity Reports, 11*(4), 263–276. https://doi.org/10.1007/s13679-022-00478-w

26. Qian, Y., Xia, F., Zuo, Y., et al. (2022). Do patients with Prader-Willi syndrome have favorable glucose metabolism? *Orphanet Journal of Rare Diseases, 17*(1), 187. https://doi.org/10.1186/s13023-022-02344-3
27. Danowitz, M., & Grimberg, A. (2022). Clinical indications for growth hormone therapy. *Advances in Pediatrics, 69*(1), 203–217. https://doi.org/10.1016/j.yapd.2022.03.005
28. Irizarry, K. A., Miller, M., Freemark, M., & Haqq, A. M. (2016). Prader Willi syndrome: Genetics, metabolomics, hormonal function, and new approaches to therapy. *Advances in Pediatrics, 63*(1), 47–77. https://doi.org/10.1016/j.yapd.2016.04.005
29. Goldman, V. E., Naguib, M. N., & Vidmar, A. P. (2021). Anti-obesity medication use in children and adolescents with Prader-Willi syndrome: Case review and literature search. *Journal of Clinical Medicine, 10*(19), 4540. https://doi.org/10.3390/jcm10194540
30. Passone, C. B. G., Pasqualucci, P. L., Franco, R. R., et al. (2018). Prader-Willi syndrome: What is the general pediatrician supposed to do? — A review. *Revista Paulista de Pediatria, 36*(3), 345–352. https://doi.org/10.1590/1984-0462/;2018;36;3;00003