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THE SYNDROME OF CONSTANT HUNGER

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ABSTRACT

Prader–Willi syndrome (PWS) is a rare genetic disorder resulting from abnormalities in gene expression. The inability to experience satiety constitutes the major challenge faced by individuals affected by this condition. This lifelong disturbance manifests through numerous complications, including morbid obesity, hypogonadism, infertility, diabetes mellitus, hypercholesterolemia, arterial hypertension, cardiovascular diseases, obstructive sleep apnoea, degenerative joint disease, immobility and even social stigmatization due to excessive body weight.
The disease and its secondary complications significantly impair the quality of life and contribute to a reduced life expectancy. Although Prader–Willi syndrome is an uncommon clinical entity, the severity and complexity of its manifestations require continuous and coordinated efforts from physicians and healthcare professionals.

KEYWORDS

Prader-Willi Syndrome, Obesity, Chromosome Disorder, Metabolism, Hypothalamic Disorder

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1. Introduction

Prader – Willi syndrome was first described in 1956 by Prader, Labhart and Willi [1].

It is not a common disease; however, due to its complex pathophysiology and multifaceted course, patients typically present multiple comorbidities. The predominant symptom is obesity, resulting from hyperphagia caused by an impaired sense of satiety, along with a wide range of related complications [2].

In the past, this medical condition was often called HHHO syndrome – this acronym represented main elements of this syndrome (hypotonia-hypomentia-hypogonadism-obesity) [1].

2. Epidemiology

In Poland, Prader–Willi syndrome affects approximately 1 in 20,000 newborns, with an estimated 200 individuals currently living with the condition nationwide. Globally, the estimated number of affected individuals is 350,000–400,000 people [1]. No sex predilection has been observed, and the severity of the disease does not appear to differ between males and females [3].

3. Pathophysiology: why does Prader–Willi syndrome develop?

Prader–Willi syndrome (PWS) is a genetic disorder; however, its development does not follow the classical Mendelian inheritance pattern. The disease is classified as a microdeletion syndrome and results from abnormal regulation of gene expression caused by a spontaneous mutation. [5][6].

In physiological conditions, during gametogenesis, certain regions of DNA undergo methylation, a process that silences one of the two alleles of a given gene. In a normal gamete, the region located on chromosome 15 (specifically 15q11.2–q13) is methylated (silenced) on the maternal chromosome, while the corresponding paternal allele remains active.

In Prader–Willi syndrome this process is disrupted: the paternal copy of the 15q11.2–q13 region is not expressed, while the maternal copy is abnormally expressed. This lack of paternal gene expression may result from one of the following mechanisms [5]:

1. Deletion of the 15q11–q13 region on the paternal chromosome (most common cause),
2. Maternal uniparental disomy (UPD) of chromosome 15q11–q13,
3. Imprinting defect affecting the same region.

Although main symptoms do not differ between given mutations, there are some mild phenotypic differences. Higher body mass index, scoliosis, and more severe behavioural problems are described in those with a deletion. Those with maternal disomy generally have less distinct physical features and milder behavioural problems than those with a deletion, nevertheless those patients are more likely to exhibit autistic behaviours and are more at risk for psychosis [1].

Genetic abnormalities within the chromosomal region 15q11–q13 lead to the inactivation of several key genes essential for a normal hypothalamic function. Hypothalamic dysfunction is a central element in the pathogenesis of Prader–Willi syndrome (PWS) [4]. It involves not only hormonal deficiencies and secondary hypofunction of peripheral endocrine organs—such as pituitary gland, thyroid gland, and adrenal glands—but also impaired signalling mediated by hypothalamic neuropeptides.

Post-mortem studies have demonstrated a reduced number of oxytocin-producing neurons in the paraventricular nuclei of the hypothalamus, which may contribute to the characteristic disturbances in appetite regulation observed in patients with PWS [7].

Differences between individuals with Prader–Willi syndrome and healthy subjects are also evident in the anatomy and function of the hypothalamic–pituitary axis. Children with PWS have a pituitary gland approximately 50% smaller than their healthy peers, and is characterized by an irregular shape, reduced height and a longer pituitary stalk [7].

During puberty, the pituitary gland volume in individuals with Prader–Willi syndrome (PWS) does not increase as it does in healthy adolescents. In adults with PWS the pituitary gland remains smaller than in healthy controls, and in some cases, a partially empty sella turcica has been observed [7][8].

Studies have shown that reduced hypothalamic volume is associated with increased body mass index (BMI) in patients with PWS, but it does not correlate with intelligence quotient (IQ) or age [8]. The same study compared hypothalamic volumes between patients with PWS and obese individuals without the syndrome, confirming that obesity itself is not responsible for the reduced hypothalamic volume [7][8]. In obese subjects without PWS, no structural or volumetric abnormalities of the hypothalamus were observed [8].

Furthermore, functional connectivity between the hypothalamus and the lateral occipital complexes in both hemispheres is altered in patients with PWS. This pathway is involved in food-related reward processing and satiety perception, and its dysfunction may contribute to the preoccupation with food commonly observed in these patients. Neuroimaging studies have revealed an increased activation of these regions in response to food-related stimuli.

The lateral occipital complex (LOC) is involved in the processing of visual stimuli and the recognition of objects as potential food sources [9][10][11]. The LOC is functionally connected with the satiety center located in the hypothalamus, the reward center in the nucleus accumbens, and the impulse control center in the orbitofrontal cortex. [8]

As a consequence of the anatomical and functional abnormalities mentioned above, the secretion of neuropeptides regulating these pathways—including leptin, ghrelin, pro-opiomelanocortin (POMC) and neuropeptide Y (NPY)—is impaired. This dysregulation contributes directly to the clinical manifestations observed in patients with Prader–Willi syndrome [7].

4. Symptoms

Patients with Prader–Willi syndrome (PWS) exhibit significant disturbances in neuropeptide signalling pathways, resulting in a markedly elevated threshold for satiety perception [1][7]. This means that even after consuming food that meets or exceeds their caloric requirements, the brain fails to generate a signal to stop eating. Consequently, patients develop hyperphagia and rapid, excessive weight gain, often leading to morbid obesity and, in extreme cases, gastrointestinal rupture due to massive gastric distension.

The uncontrolled urge to eat may lead patients to ingest non-food substances that resemble food in smell or appearance, sometimes resulting in food poisoning—for example through the consumption of detergents, shampoo or stones. When caregivers restrict food access, patients with Prader – Willi syndrome may experience outbursts of rage and obsessive–compulsive behaviours.[9][10].

The hypothalamic pathways responsible for thermoregulation are also impaired, meaning that during infections, patients may not develop fever. Additionally, the pain threshold is abnormally high, leading to reduced sensitivity to injury and, in some cases, self-injurious behaviours, such as skin picking, which is frequently observed in individuals with PWS [11][12].

Dysfunction of the hypothalamic–pituitary axis results in multiple pituitary hormone deficiencies, giving rise to several clinical manifestations, including [13]:

- Reduced levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), leading to impaired growth and delayed puberty
- Hypogonadism and infertility
- Hypothyroidism
- Decreased bone mineral density (osteopenia/osteoporosis)
- Adrenal insufficiency

Phenotypically, patients are typically short in stature, have disproportionately short limbs, excess adipose tissue, and reduced muscle mass. In addition to endocrine abnormalities, intellectual disability, learning difficulties, and impaired social functioning are common. Motor development is delayed not only due to obesity but also because of hypotonia, which is present from birth [13]. This neonatal floppy infant syndrome, often accompanied by poor sucking reflex, should prompt clinicians to consider Prader–Willi syndrome in the differential diagnosis. Prenatal signs may also raise suspicion of the disorder, as fetal movements tend to be reduced, and newborns may be small for gestational age with underdeveloped genitalia [14][15].

5. Diagnosis

The diagnosis of Prader–Willi syndrome (PWS) should ideally be established in the early postnatal period. When a newborn presents clinical features suggestive of PWS, comprehensive genetic testing should be performed. The DNA methylation analysis remains the gold standard for confirming the diagnosis [16]. This method not only detects the molecular abnormalities underlying PWS but also enables differentiation between Angelman syndrome, which involves a defect in the same chromosomal region (15q11–q13) but originates from the maternal chromosome. Early diagnosis and prompt initiation of treatment are essential for improving the long-term outcomes of patients with PWS. In addition to pharmacological therapy, specialized feeding techniques and rehabilitation programs should be implemented to ensure adequate nutrition and support neurodevelopment in infants with poor sucking reflex [12].

Table 1. (based on [14][15][17][18]).

disorder	Long – term result
Hypothalamus disorder	hyperphagia thermoregulation dysfunction high pain threshold
Hyperphagia	obesity, perforation of gastrointestinal tract
hypopituitarism	Hypogonadism, infertility Short stature Endocrine gland insufficiency
obesity	Diabetes mellitus Hyperlipidemia Cardiovascular diseases Impaired mobility Obstructive sleep apnea
Sedentary lifestyle	decubitus ulcer Infections Progression of obesity Social impairment thrombosis
High pain treshold	Skin nibbling Autoagression infections

6. Is Prader Willi Syndrome treatable?

Prader–Willi syndrome is a disorder that adversely affects life expectancy. Most patients die as a result of respiratory complications (such as respiratory failure or infections), obesity-related complications or cardiovascular diseases [19]. Therefore, early diagnosis and initiation of appropriate therapy are crucial for improving prognosis for those patients.

The cornerstone of pharmacological management in PWS is growth hormone (GH) therapy. Numerous studies have demonstrated that GH supplementation should be initiated as early as possible, ideally before puberty. The typical dosage used in children is 1 mg/m² per day [13].

This therapeutic approach offers multiple benefits including [13][20][21]:

- Increased insulin-like growth factor 1 (IGF-1) concentration
- Achievement of greater final height, sometimes comparable to average population norm
- Reduction in body fat percentage with a corresponding increase in lean muscle mass
- Improved muscle strength and physical performance
- Enhanced cognitive abilities
- Reduction of cardiovascular complications

7. Conclusions

A patient with Prader–Willi syndrome (PWS) presents a challenge not only for clinicians but also for the entire healthcare system. Many medical facilities lack the specialized equipment required for the hospitalization and diagnostic evaluation of individuals with extreme body weight. This includes hospital beds with higher load capacity, patient lifts to facilitate nursing care, as well as CT scanners and MRI machines equipped with tables capable of supporting excessive weight. As a result, advanced diagnostic procedures and routine nursing care for such patients are often significantly hindered. Therefore, early diagnosis and treatment are essential to limit excessive weight gain and allow individuals with Prader Willi Syndrome to function more independently within society. Equally important is the provision of adequate psychological support, not only for the patient but also for the entire family. Unfortunately, stigmatization related to severe obesity remains a common and distressing issue faced by individuals with Prader–Willi syndrome. A proper treatment is possible only when all medical specialities and society fully understand the nature of this disease.

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