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# Management of Prader-Labhart-Willi syndrome in children and in adults, with particular emphasis on the treatment with recombinant human growth hormone

Sposób postępowania u dzieci i dorosłych z zespołem Pradera-Labharta-Williego, ze szczególnym uwzględnieniem leczenia preparatem ludzkiego rekombinowanego hormonu wzrostu

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**Abstract**
**Introduction:** Prader-Willi syndrome (PWS) is a genetically determined disease that manifests itself in a number of abnormalities resulting, among others, from dysfunction of the hypothalamic-pituitary system. Only integrated, multidisciplinary care gives patients the chance to significantly improve the quality of life and achieve a life expectancy that does not differ from the general population.
**The aim of the study** was to summarize the available literature on the management of patients suffering from PWS.
**Conclusions:** More and more reports based on clinical trials conducted around the world indicate the undeniable benefits of rhGH therapy in patients with PWS in childhood and after the end of growth period. They consist in improving the body composition, improving the lipid profile, increasing bone mineral density and improving the mental state and patients' quality of life.
**Key words:**
Prader-Willi syndrome, obesity, recombinant human growth hormone, metabolism, therapeutic program.

**Streszczenie**
**Wstęp:** Zespół Pradera-Williego (PWS) jest genetycznie uwarunkowaną chorobą, która manifestuje się licznymi zaburzeniami, wynikającymi m.in. z nieprawidłowej czynności układu podwzgórzowo-przysadkowego. Jedynie zintegrowana, wielodyscyplinarna opieka daje pacjentom szansę na znaczną poprawę jakości życia oraz osiągnięcie długości życia nieodbiegającej od populacji ogólnej.
**Cel pracy:** Podsumowanie dostępnego piśmiennictwa dotyczącego postępowania z pacjentami cierpiącymi na PWS.
**Wnioski:** Coraz liczniejsze doniesienia oparte na prowadzonych na całym świecie badaniach klinicznych wskazują na niezaprzeczalne korzyści płynące z terapii rhGH stosowanej u chorych z PWS w wieku dziecięcym, jak również w wieku dorosłym – po zakończeniu procesu wzrastania. Polegają one na poprawie składu ciała, poprawie w zakresie lipidogramu, zwiększeniu gęstości mineralnej kości oraz poprawie stanu psychicznego, a także jakości życia chorych.
**Słowa kluczowe:**
zespół Pradera-Williego, otyłość, ludzki rekombinowany hormon wzrostu, metabolizm, program terapeutyczny.

## Introduction

Prader-Willi syndrome (PWS), or actually Prader-Labhart-Willi syndrome is a genetically determined disease that manifests itself in a number of abnormalities resulting, among others, from dysfunction of the hypothalamic-pituitary system. Only integrated, multidisciplinary care gives patients the chance to significantly improve the quality of life and achieve a life expectancy that does not differ from the general population. The aim of this study was to summarize the available literature on the management of patients suffering from PWS.

## Historical background

The disease in question was first described in 1956 by Swiss doctors Andrea Prader, Heinrich Willi and Alexis Labhart. The description concerned nine patients, who were diagnosed with growth deficiency, obesity, mental retardation, and small



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hands and feet [1]. In the past, this medical condition was often called HHHO syndrome – this acronym represented the main elements of the syndrome (hypotonia-hypomentia-hypogonadism-obesity) [2].

## Epidemiology

Prader-Willi syndrome occurs in 1 in 10,000-30,000 live births, and affects females and males equally [3]. It is considered a rare disease, but numerous reports indicate that it is one of the most common genetic pathologies. It is estimated that every year in Poland, about 25-30 people are born with the syndrome [4]. The vast majority of the described cases of PWS result from sporadic mutations. The risk of occurrence of this syndrome in the next child in the family it is low, equal to the population risk.

## Genetic background

The cause of PWS is the loss of part of the long arm of chromosome 15 in the 15q11.2-q13 region, called the critical region [3]. The phenomenon of genomic imprinting in humans was described for the first time on the basis of this medical condition. It consists in different activity of genes depending on which parent they are inherited from. Under normal conditions, genes in the 15q11.2-q13 region inherited from the father undergo transcriptional activity, while analogous genes on the maternal chromosome become inactivated, most likely as a result of DNA methylation. In PWS, the gene product of the only active copy of these genes – the copy of paternal origin – is lost. The lost gene SNRPN (small nuclear ribonucleoproteins) codes a small nuclear riboprotein expressed in the central nervous system, as well as a SNURF polypeptide (SNRPN upstream reading frame) and the splicing factor SmN. Mutations of these genes are responsible for neurodevelopmental and endocrine disorders occurring in PWS. About 70% of PWS cases are caused by microdeletions within the above-mentioned region. Most of the remaining cases are caused by the phenomenon of single-parent disomy – a situation where both copies of a given gene come from one of the parents (in this case, the mother). About 1% of all PWS cases result from deletions within the area containing the imprinting centre – the DNA sequence responsible for the correct course of the imprinting phenomenon. Finally, less than 1% of cases are situations in which there is a balanced chromosomal rearrangement within the 15q11.2 – q13 region [3]. It should be mentioned that when the deletion in the analogous region of chromosome 15 took place in the genetic material inherited from the mother, Angelman syndrome develops.

## Diagnostics

Due to the relatively rare occurrence of the disease and the different severity of both dysmorphic features and other components of the syndrome, the early diagnosis of PWS may be difficult. The diagnosis of PWS is based primarily on the clinical picture. The diagnosis requires confirmation by cytogenetic examination. In the molecular diagnostics of the syndrome, the FISH method (fluorescence in situ hybridization), DNA methylation analysis and DNA sequencing are used. In the case of PWS, also prenatal diagnosis is possible [3].

The clinical diagnosis of PWS is facilitated by the scale created by Holm *et al.* published in 1993 [5]. According to it, the symptoms accompanying the discussed syndrome were divided into larger (each of them is given 1 point), smaller (each of them gives 0.5 points) and non-scored auxiliary symptoms. In order to diagnose PWS in a patient under 3 years of age the sum of the points has to be at least 5 (of which at least 4 points should come from the larger criteria), and the diagnosis of a patient above 3 years of age requires at least 8 points (of which at least 5 points should be higher criteria).

**The major criteria include:**

- low muscle tone and sucking difficulties (and subsequent feeding problems) in the first year of life;
- small weight gain in infancy;
- increased appetite and disorders of satiety starting from the second year of life;
- rapid weight gain after the second year of life, leading to obesity;
- characteristic dysmorphic features: narrow face, almond-shaped eyelid fissures, small mouth, thin upper lip, downward corners of the mouth;
- hypogonadism – in boys, small testicles, small penis and poorly developed scrotum, often cryptorchidism; in girls, a small clitoris, hypoplastic labia minora;
- psychomotor retardation in patients under the sixth year of life, moderate or mild mental retardation later in life;
- diagnosed cytogenetic abnormalities within the 11–13 region on the long arm of chromosome 15.

**The minor criteria include:**

- reduced mobility in the fetal and neonatal period, which improves with age;
- weak scream;
- behavioural disorders: tantrums, quarrelsomeness, obsessive behaviour, mood changes, outbursts of aggression, stubbornness, tendency to lie and steal;
- sleep disturbances and sleep apnea;
- short stature in relation to the height of the parents;
- skin and hair hypopigmentation compared to other family members;
- small hands ($< 25^{th}$ percentile for age) and feet ($< 10^{th}$ percentile for age);
- narrow hands with a straight elbow edge;
- thick, sticky saliva and cracking of the skin at the corners of the mouth;
- tendency to pick at the skin;
- speech disorders (articulation disorders);
- ophthalmic disorders (strabismus, myopia).

The auxiliary criteria include: thermoregulation disorders, lowered pain threshold, reduced tendency to vomiting, scoliosis or deepened kyphosis of the spine, early adrenarche, osteoporosis, high efficiency in arranging puzzles as well as a correct EMG test result.

## Clinical picture

PWS is a multi-system disease and its clinical manifestation depends on the patient's age. The earliest symptom of the syndrome is low muscle tone, which manifests itself in the fetal period as impaired fetal movements. Additionally, children with PWS often show intrauterine growth retardation and low birth weight. After giving birth, there occur feeding difficulties due to the disturbed suckling reflex. Patients often require feeding via a nasopharyngeal tube. Another feature visible in the early stages of a child's life is hypogonadism – in girls it manifests itself with poor development of the labia minora and the clitoris, while in boys it manifests itself with cryptorchidism and scrotal hypoplasia [6]. It seems that genetic background in children with PWS have little impact on perinatal data [7].

Later in life, among girls, primary amenorrhea may be observed, while boys have decreased testicular and scrotal volume and the presence of a small penis and, at the same time both gender have delayed and incomplete puberty. The vast majority of patients are infertile. A direct consequence of the deficiency of sex hormones is osteoporosis. Growth hormone deficiency also contributes to low bone mass. Hypogonadism in PWS is most often of hypothalamic origin, however, in some male patients, primary hypogonadism is also observed [8]. Approximately 15–30% of children with PWS have early adrenarche (increased secretion of androgens by the adrenal cortex, preceding sexual maturation), which may be secondary to obesity and result from the effect of high insulin levels on the adrenal cortex [9].

Accelerated weight gain in patients with PWS develops typically after the second year of life, which, in the absence of appropriate actions – usually before the age of 6, leads to the development of simple obesity [10]. The prevalence of obesity in these patients increases with age. According to various reports, among adult patients, the percentage of obese people is as high as 82–98% [10]. Complications related to excess body weight are the main cause of death of PWS patients. These include obstructive sleep apnea syndrome, type 2 diabetes, steatohepatitis, cardiopulmonary insufficiency, and thromboembolism [11]. The immediate cause of obesity is hyperphagia resulting from inborn damage to the hunger and satiety centre neurons in the hypothalamus. After eating a meal, patients do not feel full. Additionally, patients have increased levels of ghrelin (the neurohormone that stimulates the appetite) and leptin resistance [11–13].

It is worth mentioning the typical dysmorphic features that become more pronounced as the child grows – patients often have a narrow face, antimongoid eye position, almond-shaped eyelid slits as well as a thin upper lip and downward corners of the mouth. Additionally, acromicry is observed, i.e. small hands and feet with toes narrowing towards the ends. Moreover, there may occur strabismus, hypopigmentation of the skin, irises and hair, and thick saliva favouring the development of caries [3].

Particular attention should be paid to the growth hormone deficiency (GHD) in PWS. Patients have decreased levels of insulin-like growth factor 1 (IGF-1) as well as decreased GH secretion, both under baseline conditions and in stimulation tests. According to various reports, 40–100% of children with PWS meet the criteria for GHD [4]. In the adult patient population, this percentage is 40–50% [14]. Apart from the obvious consequence of the lack of growth hormone, which is a reduction in growth rate, short final height (on average 150 cm in women, 160 cm in men) and delayed maturation of the skeleton, GHD results in a number of metabolic disorders and changes in body composition [14]. GH is responsible for regulating protein synthesis as well as lipolysis, therefore in the case of its deficiency, typically the proportion of fat body mass increases at the expense of lean mass. This causes muscle weakness and contributes to a reduced basic energy requirement, which promotes obesity. There occurs also a reduced mass of the left ventricular muscle. Growth hormone deficiency also promotes lipid disorders (increased levels of total cholesterol, triglycerides and LDL cholesterol fraction together with a reduction in HDL fraction), which in turn leads to the development of cardiovascular diseases [15]. Additionally, the deficiency of this hormone results in disturbances in bone mineralization. Disorders of carbohydrate metabolism among children with PWS are rare, but with age, the percentage of patients with insulin resistance and type 2 diabetes increases. It is estimated that as many as 25% of patients over 20 years of age develop type 2 diabetes, and its incidence significantly correlates with patients' BMI [4].

The typical symptoms of PWS are behavioural changes also showing a tendency to increase with age. The most common of these are mood changes, aggressive behaviour, tantrums, irritability, compulsive behaviour, and poor social interaction. Children are often capricious, stubborn and prone to quarrels. They show little flexibility in behaviour and are reluctant to accept any changes in their familiar routine. Additionally, about 20% of patients exhibit behaviours typical of autism spectrum disorders [16]. The vast majority of patients show a delay in psychomotor development from early infancy, and later in life they are diagnosed with mild (about 1/3 of patients), moderate (27% of patients) or severe (6% of patients) mental retardation. The remaining patients are characterized by an IQ at the lower end of the population norm, however, due to significantly impaired social abilities, most of them are unable to function independently and require constant supervision by their caregivers [16].

Speech in children with PWS develops later than in healthy peers, and patients often have articulation disorders. Disturbances in cognitive functions and short-term memory are also observed as well as numerous psychiatric problems (mainly mood disorders and psychosis) [3, 4,16].

Other features of the syndrome include an increased pain threshold as well as disturbances in thermoregulation, namely inclination both for hypo- and hyperthermia. Sleep problems are also often observed as well as sleep apnea syndrome [3].

Disturbed secretion of neurohormones in PWS patients, leading to GHD and hypogonadotrophic hypogonadism, decreased muscle tone, lack of satiety, high pain threshold and disturbances in thermoregulation all result from damage to the hypothalamic-pituitary area. Hypothalamus dysfunction is

 

also the cause of impaired gag reflex and frequent urination at night [3].

Hypoplasia or ectopy of the posterior pituitary gland and sometimes a reduction in the hypothalamic nuclei, have also been reported in many PWS patients [17].

About 20–30% of children with PWS develop hypothyroidism. In most cases, it is secondary hypothyroidism - a decreased concentration of free thyroxine (FT4) in the serum is accompanied by normal or low TSH levels [3,18]. In adult patients, the percentage of patients with hypothyroidism is similar to that observed in the general population. Another consequence of the malfunction of the hypothalamus is secondary adrenal insufficiency in some patients (there are no precise data on the frequency of this phenomenon; according to various reports, it affects 10–60% of patients) [19]. It manifests itself mostly in stressful situations, which indicates a decreased adrenal reserve – the concentrations of morning cortisol and ACTH in basic conditions are usually not lowered.

The life of untreated PWS patients is significantly shorter than in the general population. Increased mortality is already observed among patients under 18 years of age. Deaths from respiratory failure, infection and choking are the most common in this age group [20].

## Treatment

There is no causal treatment for PWS, therefore management is limited to controlling the symptoms of the disease, preventing its complications and improving the quality of patients' life. Care for patients with PWS should be taken in a comprehensive manner and include treatment with a human recombinant GH (rhGH) preparation as well as intensive dietary treatment, daily physical activity, rehabilitation classes together with the care of a psychologist and speech therapist. As mentioned earlier, obesity is the dominant symptom of PWS, which favours the development of individual components of the metabolic syndrome (hypertension, carbohydrate disorders, dyslipidemia) among patients. It is these factors that contribute to the increased mortality and shorter life expectancy in patients with this syndrome. Therefore, prevention and treatment of obesity is the overarching goal of caring for patients with PWS. The constant feeling of hunger, behavioural disturbances and low physical activity contribute to the lower effectiveness of dietary techniques applied. In addition, it should be emphasized that patients with PWS have a significantly lower caloric requirement and are shorter compared to healthy peers of the same sex due to the reduced muscle mass [21].

Earliest possible introduction of intensive dietary management combined with the education of caregivers significantly increases the chance of stopping excessive weight gain. Dietary and psychological counselling plays an important role in caring for patients and their families. The diet of PWS patients should be balanced, varied and based on products with a low glycemic index. It is recommended to limit the caloric content of meals to approximately 70–80% of the recommended daily caloric intake for specific sex and age, respectively [21, 22]. Meals should be small and eaten at regular intervals, preferably at fixed times. The following proportion of macronutrients in the diet is proposed: 45% carbohydrates, 30% fats and 25% protein. Additionally, the fiber intake should be at least 20 g per day. It is considered that the composition of the optimal diet for PWS patients should be similar to the Mediterranean diet [21, 22]. Caretakers should prevent patients' access to places where food is kept. The role of behavioural interventions aimed at reducing the stress associated with the almost constant feeling of hunger is also emphasized. Patients should be regularly weighed and controlled in a dietary clinic.

Apart from the diet, the key element of PWS management is physical activity. Daily exercise activities supervised by caregivers not only increase energy expenditure, but also contribute to the increase of the muscle mass – thus increasing the resting metabolic rate. In addition, these activities improve motor coordination and muscle tone, and by involving the patient, distract him/her from the feeling of hunger. Due to the low muscle tone, physical activity should be carried out under the supervision of an experienced physiotherapist.

The procedure described above should be implemented as early as possible – the best results are achieved by starting an obesity prevention program before the patient develops hyperphagia. Kimonis *et al*. emphasize that early diagnosis of PWS, enabling the fastest possible implementation of appropriate measures, is of key importance for the long-term effects of treatment of the above mentioned patients [23]. It not only delays the onset of obesity and its complications, but also extends the life of patients and significantly improves its quality.

Due to the frequently observed ineffectiveness of conservative management, mainly due to non-compliance with medical recommendations, attempts are made to introduce pharmacological treatment into the treatment of obesity in the course of PWS. Phase II and III clinical trials have demonstrated the efficacy, safety and good tolerability of the glucagon-like peptide 1 (GLP-1) analogs, exenatide and liraglutide in the treatment of simple obesity. However, Tan *et al.* [24] emphasize that the results of randomized, double-blind clinical trials assessing the effectiveness of GLP-1 analogues in the treatment of obesity in the course of PWS have not been published so far. Numerous case reports of PWS patients receiving exenatide or liraglutide therapy available in the literature suggest their beneficial effect on reduction of appetite and a sustained reduction in the BMI [25, 26]. The above indicates the need for further research in this direction.

Oxytocin is a hormone proven to reduce the feeling of hunger, and also influencing social bonds building. Its significantly decreased concentrations are observed in the course of PWS [27, 28]. Clinical trials are currently underway to assess safety and effectiveness of oxytocin and its analog (carbetocin) in the treatment of hyperphagia and behavioural disorders in PWS patients. Preliminary results indicate their beneficial effect on weight loss and improvement in social behaviour with good treatment tolerance and no significant side effects [28, 29].

High hopes are associated with the molecularly targeted preparation AZP-531, which is an analog of the non-acetylated

form of ghrelin. This drug exerts an antagonistic effect on ghrelin (a neurohormone that contributes to hyperphagia in PWS patients). Clinical trials are currently underway to assess livoletide effect on weight loss among the patients [30].

It is also postulated that diazoxide (a drug used so far in conditions with autonomic hyperinsulinism) is effective in reducing appetite and the amount of visceral fat as well as it contributes to reducing cardiovascular risk and increasing insulin sensitivity [31].

Orlistat (pancreatic lipase inhibitor), due to its troublesome side effects, did not turn out to be an attractive therapeutic option for patients with obesity in the course of PWS [32].

Metformin is widely used in patients with PWS, both in the treatment of insulin resistance and in the treatment of type 2 diabetes [33]. It appears that this drug may reduce appetite, however, there are no certain data on this subject so far [22, 24].

Surgical treatment of obesity is being attempted in adolescent patients suffering from PWS. Patients with BMI above 35 kg/m$^2$ with associated severe conditions, such as obstructive sleep apnea with moderate to severe intensity, type 2 diabetes, pseudo-brain tumor or severe and progressive steatohepatitis, are considered candidates for bariatric treatment [3]. Additionally, surgical treatment of obesity may be considered for patients with BMI higher than 40 kg/m$^2$ and with at least one comorbid disease typical of this syndrome [3]. Currently, the most frequently chosen method is sleeve gastrectomy, less often gastric excision with Roux-en-Y anastomosis. Reports on the effectiveness of such treatment are contradictory. Some authors (Inge 2020, Yuk-Wah Liu *et al*. 2020) indicate the unsatisfactory effectiveness of these procedures in weight reduction in long-term follow-up as well as numerous surgical and metabolic complications of these operations [34, 35]. On the other hand, Alqahtani *et al*. in their work on laparoscopic sleeve gastrectomy emphasize the high effectiveness of this procedure, measured by a permanent reduction in BMI, resolution or alleviation of the course of comorbidities (arterial hypertension, lipid disorders, carbohydrate disorders, obstructive sleep apnea), without the observed increase in mortality and other significant complications [36]. Certainly, this form of treatment should be considered in patients with morbid obesity in the absence of the effectiveness of conservative management. Taking such decision requires special caution, as the persistent increased appetite after the surgery may significantly reduce the effectiveness of the procedure and increase the risk of complications. The need for constant psychological and dietary care in patients with PWS after bariatric surgery should be emphasized in order to avoid nutritional deficiencies and other undesirable effects of this therapy.

Many patients with PWS require hormonal treatment to induce puberty and maintain its normal course. This treatment also has a positive effect on bone mineral density, muscle mass, mental performance, emotional stability and overall quality of life. Currently, there are no recommendations regarding the treatment of hypogonadism in patients with PWS, however, it is widely believed that the dosage of individual hormonal preparations and the time of their inclusion should reflect the physiological process of normal sexual maturation. Hormone replacement therapy (HRT) should be continued in adult patients as it prevents bone loss.

In patients of all age groups, in addition to hormonal treatment, calcium and vitamin D3 should be supplemented to maintain normal bone mass. Periodic densitometric tests are also recommended [3]. It is believed that transdermal preparations should be the preferred form of estrogen-progestin therapy. Not only are they better tolerated, but also (unlike oral preparations) they do not affect the hepatic metabolism of GH. In addition, transdermal devices reduce the risk of metabolic complications of HRT. Treatment with testosterone in male patients generally starts with 50 mg intramuscularly every 4 weeks (approximately 33–50% of the dose recommended for adult men with hypogonadism) [3]. This dose is gradually increased under the control of clinical symptoms and testosterone levels in the serum. Due to the tendency of patients with PWS to nibble the skin (hindering optimal treatment with transdermal preparations), the intramuscular route of administration is preferable. Patients should be monitored for aggressive behaviour, which, however, is not often described after the initiation of testosterone treatment. It should be mentioned that among boys with PWS the occurrence of cryptorchidism is at high level (over 80% of patients). The testicles should be placed in the scrotum during the first year of life [3].

The rules of treating hypothyroidism in patients with PWS do not differ from the rules adopted for other patients. Due to the fact that in the vast majority of patients secondary hypothyroidism is observed, the therapy should be guided by the concentration of FT4, which should be in the upper range of normal values. It is suggested to measure TSH and FT4 levels in all patients as soon as possible after the diagnosis of PWS, and then control these tests every 6–12 months [3]. It should be remembered that in patients treated with rhGH, the conversion of T4 to T3 increases, which lowers the concentration of FT4 in the serum. Therefore, after the initiation of therapy with the preparation of rhGH and each time after changing its dose, the thyroid-metabolic state of the organism should be checked after 6 weeks.

Due to the decreased adrenal reserve in some cases of the syndrome, empirical administration of 'stress doses of glucocorticosteroids' has been suggested to patients in the case of acute infections, injuries and surgical procedures in any case, in which adrenal insufficiency was not excluded. Caregivers of patients with PWS should be thoroughly informed about the symptoms of hypocortisolemia and the management of such symptoms [3]. It is important to emphasize that disturbances in thermoregulation and impaired gag reflex are responsible for the incomplete picture of adrenal crisis in these patients.

The need for constant psychological care in all patients with PWS should be mentioned. Workshops of occupational therapy conducted by qualified persons experienced in working with PWS patients are also beneficial. Because even among children with a normal IQ, the vast majority have problems with learning, patients require special support both at educational institutions and at home.

 

Due to comorbid mental disorders, some patients with PWS require treatment with psychotropic drugs, however, a detailed discussion of such procedures is beyond the scope of this study.

## Treatment with recombinant human growth hormone (rhGH) preparation

Treatment with rhGH is currently the only pharmacological treatment that has proven long-term efficacy in preventing complications of PWS and prolonging the life of patients with this diagnosis. This treatment was approved in Europe for PWS patients in 2001. Approx. 80% of PWS patients who do not receive GH therapy die between the age of 11 and 40. The inclusion of this treatment reduces the annual mortality of patients from 3% to about 1.25%.

Proffitt *et al.* analyzed a group of over 2,000 patients with PWS, comparing the clinical parameters and the treatment implemented in living and deceased patients (the mean age of patients at death was 31.6 years). The living patients received rhGH therapy three times more often than those who died prematurely [10].

The obvious effect of the GH action is its proliferative impact on the growth cartilage, which results in bone growth in length. Treatment enables achievement of final height within the population norms (above the 10th percentile for sex and age), protecting patients from the psychological consequences of a height significantly different from that of healthy peers. It is believed that the main goal of treating PWS patients with rhGH is to take advantage of the beneficial metabolic effects of this therapy. Growth hormone significantly affects the disturbed body composition in these patients - the proportion of lean body mass increases (through anabolic effect on muscle tissue) at the expense of reduced adipose tissue content (lipolytic effect of the hormone on subcutaneous and visceral adipose tissue). The result is an improvement in muscle strength and muscle tone, which promotes increased physical activity, improves rehabilitation results and also increases basal metabolism, contributing to obesity prevention. Moreover, through the production of IGF-1 in osteoblasts, GH has a beneficial effect on bone mineralization [37, 38]. In addition, as a result of the therapy, the plasma lipid profile is improved – the concentration of HDL cholesterol in the serum increases and the concentration of total cholesterol, triglycerides and LDL is lowered [37, 38]. This is triggered by the lipolytic effect of the somatotropic hormone. Growth hormone also significantly affects the respiration path, reducing the number of night apnea. There are reports about beneficial effects of rhGH therapy on the IQ and improvement of cognitive abilities as well as improving patients' mood and general quality of life. An increasing number of patients, depending on their intellectual abilities, continues their education up to the secondary school stage and takes an active part in occupational therapy workshops [37].

Passone *et al.* in 2020 published systematic review of clinical trials on the effects of rhGH treatment in both children and adult patients [14]. It included both patients with documented GHD and without such deficiency. Based on this study, it was found out that the vast majority of studies taken into account proved that rhGH therapy significantly increased the growth rate and final height compared to the control group, which did not receive this treatment [14]. Moreover, in the study group, it was proved that there was a lower percentage of adipose tissue in the total body weight, a higher mass of muscle tissue and a significantly lower BMI. It seems that rhGH therapy did not lead to a decrease in body mass index, but rather prevented its increase, which means a beneficial effect on the natural course of the disease. Some of the analyzed clinical trials also indicated an improvement in cognitive abilities in patients treated with rhGH [14].

The need to implement the therapy as early as possible is emphasized, optimally around the age of 2–4, before the child develops excessive appetite and obesity. According to some authors, it is beneficial and safe to start the treatment earlier, as early as between 6$^{th}$ and 12$^{th}$ month of life.

Magil *et al*. compared the height, metabolic and endocrine parameters of children who were administered rhGH treatment before and after attaining the age of 1, observing a statistically significant beneficial effect of early initiation of therapy on both the growth rate and the plasma lipid profile as well as glucose metabolism [39]. In the group of children who started therapy before attaining the age of 1, significantly lower levels of LDL cholesterol and fasting insulin were noted after attaining the age of 5 as well as a lower HOMA-IR index than in the group of patients who started treatment after the first year of life. There were no differences in the BMI, IGF-1 concentration and also in the body composition between the two groups [39]. Before starting the therapy, it is necessary to introduce intensive conservative management (diet, physical activity, rehabilitation) as well as comprehensive education of patient's caregivers. Due to the risk of increased breathing disorders during rhGH therapy, an laryngological consultation is necessary before starting it. It is also recommended to perform a polysomnographic examination. The risk of night apnea is increased by obesity, restrictive lung diseases (exacerbated by sarcopenia), scoliosis and a tendency to central sleep apnea occurring in many patients with PWS. Some studies indicate an increase in the severity of apnea during rhGH therapy, which is explained by the hypertrophy of the lymphatic tissue of the nasopharynx dependant on the increase in the concentration of IGF-1. At the same time, many researchers emphasize the improvement regarding central apnea occurring during rhGH therapy [40, 41].

In 2006, the Program of Treatment of Children with PWS with Growth Hormone was introduced in Poland, financed from public funds until the age of 18. In 2016, the reimbursement of rhGH therapy was extended to the group of adult PWS patients who received growth hormone treatment before the age of 18. Patients are qualified for the *Program* by the Coordination Team for Growth Hormone Application appointed by the President of the National Health Fund (NHF).

The criteria for inclusion in the Program of Treatment of Children with PWS with Growth Hormone in Poland include [40]:

- diagnosis of PWS based on the clinical picture, taking into account the criteria included in the Holm scale. The diagnosis has to be confirmed by genetic testing;

- patient's age under 18;
- bone age under 16 in girls and under 18 in boys;
- body mass index (BMI) less than the 97$^{th}$ percentile for sex and age; at least 6 months of observation in a treatment centre is required (it is considered that in the case of young children who have not yet developed excessive body weight this requirement is not justified);
- lack of carbohydrate metabolism disturbances determined on the basis of a correct result of the oral glucose tolerance test (with determination of the concentration of both glucose and insulin);
- conducting a laryngological consultation;
- conservative treatment for at least 6 months – dietary management and rehabilitation;
- in the case of comorbidities and other complications of PWS, conducting appropriate consultations and performing appropriate additional tests;
- lack of other contraindications to the inclusion of the rhGH treatment.

It is worth emphasizing that growth deficiency is not a necessary condition to start rhGH therapy in PWS patients. This is due to the fact that the main goal of GH treatment in this group of patients is to compensate for metabolic disorders resulting from GH deficiency. For this reason, it is not recommended to routinely perform a GH stimulation tests before starting the therapy. However, as part of qualification for the Program, IGF-1 concentration determination is required [40].

Contraindication to treatment with rhGH constitutes excessive body weight (exceeding 2 standard deviations), untreated severe obstructive sleep apnea syndrome, poorly controlled diabetes, active neoplastic disease, symptoms of increased intracranial pressure and active psychosis.

The rhGH preparation is administered daily at bedtime in subcutaneous injections in a dose 0.18–0.47 mg/kg bw/week (0.54–1.4 IU/kg bw/week). Sensitivity to GH varies in particular stages of life – much greater sensitivity occurs in very early childhood. In addition, an increase in the incidence of sudden death has been reported, mostly observed in the first 9 months after starting the treatment. Therefore, it is recommended to start with lower doses (0.009–0.012 mg/kg bw/day) and gradually increase them under the control of clinical symptoms and IGF-1 concentration, which should be in the upper normal range. Increased IGF-1 concentration as well as increased IGF-1/insulin-like growth factors - binding protein 3 (IGF-BP3) ratio raises the risk of side effects, especially the severity of sleep apnea and carries the risk of development or recurrence of previously treated neoplastic disease. A phenomenon observed in PWS cases are relatively high IGF-1 concentrations despite relatively low doses of rhGH, which indicates the need for regular monitoring of these patients.

An important issue is the need for regular monitoring of all patients during rhGH therapy:

- after 30 days from the implementation of the treatment, a laryngological consultation should be conducted;
- the above consultation should be repeated 90 days after starting the treatment together with the IGF-1 concentration control;
- every 90 days PWS patients receiving rhGH treatment are recommended to undergo monitoring in a treatment centre (24-hour hospitalization or outpatient visit), within which dietary and rehabilitation consultations should be carried out;
- every 180 days it is required to determine the concentration of TSH, FT4, ionogram and glucose in serum;
- once a year, the complete lipid profile (total cholesterol, triglycerides, LDL and HDL cholesterol fractions), percentage of glycated hemoglobin ($HbA_{1c}$) and IGF-1 concentration should be determined together with performing the oral glucose tolerance test (OGTT) with the assessment of glucose and insulin levels;

The laryngological and psychological consultations should be conducted once a year (assessment of psychomotor development in children under 7 years of age; in older patients – assessment of intellectual development). Additionally, the assessment of bone age based on wrist and hand X-ray is required once a year. Girls over 10 years of age once a year should be assessed by a gynecologist experienced in working with children.

Individual groups of patients require additional tests to be carried out every 365 days:

- children with defects of the cardiovascular system – consultation with a cardiologist and ultrasonography of the heart;
- in the case of suspected slipped capital femoral epiphysis – orthopedic consultation and imaging of the hip joints (X-ray or ultrasonography, if necessary also CT or MRI of the hip joints);
- in patients with pubertal disorders – test with intravenous gonadoliberin released hormone (GnRH) administration measurements of FSH and LH levels and 1 measurement of estrogens and androgens);
- in patients with congenital defects of the urinary system or with recurrent infections of the urinary system – urological consultation, nephrology consultation, general examination of urine and urine culture as well as ultrasonography of the abdominal cavity;
- in the case of symptoms of a pseudo-brain tumor – ophthalmological consultation, neurological consultation and imaging examination of the central nervous system (MRI or CT scan with contrast).

The patient's documentation with all test results contained therein should be presented each time at the request of the NHF controllers.

Among the side effects of rhGH therapy, disturbances in carbohydrate metabolism, resulting from the insulin-antagonistic effect of GH are often mentioned. This complication is much more common in adult patients – usually elevated fasting glucose and insulin levels are observed, with no effect on the level of $HbA_{1c}$. Glucose tolerance disorders are the most common, and type 2 diabetes is much less common. In patients undergoing the GH therapy, Vogt and Emerick [41] proposed annual monitoring of glucose, insulin and $HbA_{1c}$ levels and additionally consideration of OGTT in obese patients, patients over 12 years of age and in people with a family history of type 2 diabetes.

 

It should be remembered that rhGH therapy may lead to water retention in the body, and also to hypertrophy of the lymphoid tissue of the nasopharynx, which in the case of existing breathing disorders will adversely affect the number of apnea. In critically ill patients and in monstrously obese patients with severe night apnea, treatment with rhGH may significantly increase the risk of death [15, 41].

As mentioned earlier, due to the increased peripheral conversion of T4 to T3 by GH, in patients with subclinical hypothyroidism, treatment with rhGH may reveal hypothyroidism, while in patients previously treated with L-thyroxine, the dose of the drug may need to be increased.

Growth hormone reduces the activity of 11β-hydroxysteroid dehydrogenase type 1 – the enzyme responsible for the conversion of cortisone into cortisol. Additionally, it is believed that after starting rhGH treatment, the hepatic cortisol clearance increases, which in predisposed patients may reveal adrenal insufficiency. Therefore, before starting the treatment, it is recommended to perform at least the determination of the level of morning serum cortisol and optimally a stimulation test with synthetic ACTH for the assessment of adrenal reserve. A similar procedure is recommended before the inclusion of L-thyroxine due to the obvious fact of increased metabolism of cortisol by thyroid hormones [15].

In addition, scoliosis may develop or worsen during the treatment with rhGH, especially if growth acceleration is accompanied by rapid weight gain. However, this postural defect is not considered a contraindication to treatment with rhGH.

Treatment with rhGH should be discontinued in the following situations [40]:

- lack of proper cooperation with the patient or their caregivers;
- occurrence of the previously discussed complications of the therapy;
- cessation of dietary treatment or rehabilitation by the patient;
- occurrence or worsening of night apnea;
- occurrence of diabetes;
- increase in obesity despite properly conducted rhGH therapy and conservative management, defined as an increase in BMI by at least 2 standard deviations for sex and age.

A pseudotumor of the brain is very rarely described as a complication of growth hormone treatment. Its occurrence requires immediate termination of therapy.

Due to the beneficial metabolic effects of GH, treatment with rhGH should be continued after the end of growth. Only 40–50% of adult PWS patients meet the criteria for the diagnosis of GHD [40]. However, treatment with rhGH has been shown to bring many benefits also in people who are not GH deficient. Damen *et al*. in 2020, based on a 3-year observation of patients with PWS who continued treatment with rhGH after reaching their final height, proved that this treatment allows to maintain the beneficial changes in body composition obtained thanks to the therapy conducted in developmental age [42]. Additionally, in the group of patients whose treatment was discontinued after the end of their growth, a significant increase in the amount of adipose tissue was observed after one year. This effect was completely reversible upon re-administration of the growth hormone therapy. No significant adverse effects of treatment were described in the study group. As in the pediatric population, rhGH has an effect on the increase in muscle mass and a decrease in the percentage of body fat in total body weight in adult PWS patients. In 2015, Vogt and Emerick published a mentioned above review of the literature available at that time on the rhGH treatment among adult PWS patients [41]. A similar analysis was carried out in 2012 by Sanchez-Ortiga *et al*. [43]. The numerous evidence presented supported the thesis about the aforementioned favourable changes in body composition, but without changes in BMI. Significant changes in plasma lipid composition have not been proved unquestionably, although some studies indicated an increased HDL fraction as a result of rhGH therapy. Most of the analyzed studies also showed that GH had a beneficial effect on skeletal muscle function, increased exercise tolerance, led to an increase in the left ventricular mass, and improved cognitive abilities and overall quality of life. The most frequently reported side effects of treatment were edema of the lower limbs and insulin resistance (levels of both glucose and fasting insulin). Conflicting reports concerned the effect of rhGH on obstructive sleep apnea, which no doubt requires further research. It should be emphasized that the clinical trials currently available cover a short period of observation, and some of them were conducted in a small group, without a control group. Therefore, it is necessary to conduct many years of randomized clinical trials to evaluate the long-term effects of GH treatment.

As mentioned earlier, in 2016, the reimbursement of rhGH therapy in Poland was extended to the group of adult PWS patients who received GH treatment before the age of 18 [40]. Thus, Poland became the first country to pay for this type of treatment of adult patients from public funds. Care for child patients with PWS should be continued in multidisciplinary centres experienced in the treatment of adult patients. For adult patients with PWS who have not started rhGH treatment before reaching the age of majority, this therapy is available only for full payment, unless these patients simultaneously meet the criteria for inclusion in the National Program of Severe Growth Hormone Deficiency Treatment in Adults and Adolescents after Completion of Growth Promoting Therapy [44].

Detailed rules for the management of adults with PWS were included in the guidelines of the Polish Society of Endocrinology and the Polish Society of Pediatric Endocrinology and Diabetology published in Polish Journal of Endocrinology in 2018 [15]. They emphasize the need to continue the previously described comprehensive conservative procedure (dietary treatment, rehabilitation and physical activity) together with psychological and psychiatric care. The principles of dietary management in adult patients with PWS do not differ from the same principles for child patients. A balanced diet is recommended with a reduced caloric supply (1000–1400 kcal/d), based on products with low glycemic index.

The most common cause of death in the course of PWS after the end of growth process are cardiovascular diseases, obstructive sleep apnea, diabetes, adrenal insufficiency and gastric perforation caused by uncontrolled consumption of large amounts of food [20].

The main goal of adults' treatment, as in the case of the pediatric population, is to prevent obesity and its complications, which contribute to the increased mortality of patients. In addition to comprehensive conservative management, the most important element of preventing metabolic complications in the course of PWS is therapy with a preparation of rhGH. Contraindications to rhGH therapy among adults and the termination criteria for the therapy are the same as for the pediatric population. It needs to be highlighted that, that the treatment after the age of 18 is reimbursed only as a follow-up of the treatment during the growing period.

Due to the lower demand for GH in adult patients (the so-called metabolic doses are significantly lower than the doses promoting growth), it is suggested to reduce the dose of rhGH to about 30–50% of the dose used in children. If the therapy is started in adulthood (non-reimbursed treatment), it is recommended to start with the dose of 0.1–0.2 mg/day, with its gradual increase. The maximum dose is 1.6 mg/day.

It is necessary to regularly assess IGF-1 and IGFBP-3 levels during the GH therapy. IGF-1 concentration should be in the upper range of normal values.

Vogt and Emerick [41] suggest the evaluation of IGF-1 annually and 6 months after each rhGH dose change. Moreover, they recommend checking thyroid function within 3–6 months from starting therapy and subsequently every 12 months. Once a year, blood pressure, lipid profile, liver function parameters, $HbA_{1c}$, glucose and fasting insulin should be assessed, and OGTT should be performed in people at risk of developing type 2 diabetes. In addition, the authors emphasize the need to conduct anthropometric measurements every 6 months – these include body weight, BMI and waist circumference. Assessment of lower limb edema and symptoms of sleep apnea is recommended at each follow-up visit [41].

## Summary

Prader-Labhart-Willi syndrome is a multi-system neurodevelopmental disorder of genetic origin, the pivotal symptom of which is obesity with a complex pathogenesis. Caring for a patient suffering from this disease requires a multidisciplinary approach and involves the cooperation of an endocrinologist, dietician, occupational therapist, physiotherapist and psychologist. The overriding goal of caring for patients with PWS is to prevent excessive weight gain and to treat obesity and its complications, as they are responsible for the higher mortality rate in these patients compared to the general population and significantly reduced quality of their life. Therapy with rhGH is currently the only pharmacological treatment with documented long-term beneficial metabolic effects in PWS patients. This effect is observed both in developmental age and in adult patients. More and more reports based on clinical trials conducted all over the world indicate that the benefits of rhGH therapy are undeniable also after the end of growth period. They mainly consist in improving the body composition of patients by reducing the amount of adipose tissue in favour of lean body mass. Additionally, favourable changes in the lipid profile are observed together with increased bone mineral density. Other significant effects include the improvement of mental state, intellectual performance and the quality of life subjectively assessed by patients. So far, the effects of rhGH therapy in adult patients have been assessed only on the basis of several years of observation. Multiple years of randomized clinical trials are necessary to assess the long-term effects of rhGH treatment. In 2006, the Program for the Growth Hormone Treatment for Children with PWS was introduced in Poland, financed from public funds until attaining the age of 18. Thanks to the extension in 2016 of its reimbursement to adult patients, it is possible to significantly improve the effects of treatment in this group of patients and a significantly extend their general survival. Therapy with rhGH should be conducted in a multidisciplinary centres and accompanied by intensive conservative management for the rest of life, not only to optimize the beneficial effects of GH, but also to minimize the risk of possible side effects of rhGH treatment. Only comprehensive, integrated care gives patients a chance to significantly improve their quality of life and achieve the life expectancy not deviating from that of the general population.

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