Endokrynologia Polska
DOI: 10.5603/EP2018.0047
Tom/Volume 69; Numer/Number 4/2018
ISSN 0423–104X

Management of Prader-Willi Syndrome (PWS) in adults — what an endocrinologist needs to know. Recommendations of the Polish Society of Endocrinology and the Polish Society of Paediatric Endocrinology and Diabetology

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Abstract
Prader-Willi syndrome (PWS) is a complex genetic disorder characterised by a set of phenotypic traits, which include infantile hypotonia, short stature, and morbid obesity. Over the last 12 years, visible progress has been made in medical care management of PWS patients in Poland. Increasing awareness of the disorder in neonatal and paediatric care has led to early identification of the condition in neonates, followed by the institution of an appropriate dietary regime, introduction of physiotherapy, and early-onset recombinant human growth hormone (rhGH) treatment. Growth hormone (GH) therapy in Poland is conducted within the nationwide framework of the Therapeutic Programme: "Treatment of Prader-Willi Syndrome". The therapeutic interventions initiated in the paediatric centres need to be continued in multidisciplinary adult care settings. The main aim of PWS clinical management in adulthood is prevention of obesity and its comorbidities, treatment of hormonal disorders, mental health stabilisation, nutritional guidance, as well as on-going physiotherapy. Integrated multidisciplinary therapeutic intervention is necessary if patients with such a complex genetic condition as PWS are to not only achieve an average life expectancy but also to enjoy higher quality of life. **(Endokrynol Pol 2018; 69 (4):345–355)**

Key words: *Prader-Willi Syndrome (PWS), recombinant human growth hormone (rhGH), integrated therapy, rare diseases*

Introduction

Prader-Willi Syndrome (PWS) is a rare genetic condition, which was historically the first identified imprinting disorder in humans. The main clinical characteristics of PWS include hypotonia, developmental delay, and feeding difficulties in the first year of life. Subsequently, patients develop insatiable appetite, which in the natural history of the disease leads to early childhood obesity. The clinical picture also features hypogonadism, short stature, cognitive impairment, and intellectual disability. Symptoms of PWS result from hypothalamus dysfunction.

In recent years, there has been significant progress in the management of patients with PWS in Poland. It has stemmed from the introduction of multi-disciplinary comprehensive medical care model in close cooperation with the Polish Prader-Willi Syndrome Association, an organisation that represents patients with PWS and their caregivers, giving voice to their needs. It is justified to say that in Poland the observed phenotype of PWS has changed significantly, thanks to the early diagnoses and implementation of the comprehensive care based on physiotherapy, nutritional regime, and pharmacotherapy, which includes treatment with recombinant human growth hormone (rhGH) within the nationwide framework of the programme "Treatment of Prader-Willi Syndrome". Growth hormone therapy for children with PWS has been reimbursed since 2006;

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in 2016 the Programme was extended to adult PWS patients [1]. These developments also translate into improved psychosocial development; patients often continue their education until high school (depending on the level of intellectual disability) or take part in occupational therapy workshops. Therefore, treatment initiated in paediatric centres must be continued in multi-disciplinary medical centres for adults.

In order to support endocrinologists and other specialists providing adult care, the present paper sets out recommendations for the treatment of adult patients with PWS, developed in cooperation with the Polish Society of Endocrinology (PTE) and the Polish Society of Paediatric Endocrinology and Diabetology (PTEiDD).

Aetiology and incidence

Prader-Willi syndrome is a genetically determined condition, first described by the Swiss physicians Prader, Labhart, and Willi in 1956 [2]. It occurs in both sexes with the same frequency, affecting 1:10,000–1:30,000 live births [3]. It is associated with the loss of function of the 15q11–q13 region of the paternal allele of chromosome 15, which is referred to as the PWS critical region. The loss may be due to a deletion or other abnormality affecting the critical region on the paternal chromosome, or to maternal chromosomal disomy [4, 5]. It is estimated that between 20 and 35 children with this syndrome are born every year in Poland. Currently, the Programme of rhGH therapy covers about 180 children and eight adults with PWS. From the data obtained from the Children's Memorial Health Institute in Warsaw (CZD), approximately 80% of children with PWS, who are under the care of this centre, are treated with rhGH. One of the main conditions of inclusion in the Programme is the patient's maintaining the proper nutritional status, with a body mass index (BMI) below the 97th percentile for sex and age [1, 6–8].

The mortality rate in the population of PWS patients is higher than that found in the population of people of comparable age with mental retardation, obesity, and its complications [9]. In 2002, the mortality rate in the PWS population was estimated at 3% per year [10]. In subsequent years, following the nation-wide implementation of integrated therapy, a mortality reduction of up to 1.25% per year was observed in the same population [11].

The most common causes of death identified in children with PWS were breathing disorders, which worsened in the course of upper respiratory tract infections. This complication affects predominantly patients with pre-existing tonsil hypertrophy, which can worsen during rhGH treatment. For this reason, it is important to conduct a laryngological examination before rhGH therapy and periodically throughout the course of treatment.

Until recently, PWS patients' survival beyond their 50th birthday was a rare event. At present, following the implementation of comprehensive care model, life expectancy has risen substantially. However, in some patients (circa 15% of the PWS population) the earlier development of dementia and related disorders, characterised by faster progress than in the general population, have been observed [11].

In adult patients the most common causes of death include:

— complications of obesity (diseases of the cardiovascular system, obstructive sleep apnoea, diabetes, hypertension) [9];
— adrenocortical insufficiency (in some patients autopsy revealed small adrenal glands) [12];
— gastrointestinal perforation (typically after uncontrolled consumption of a very large meal) with delayed diagnosis due to the increased pain threshold in PWS [13].

PWS diagnosis in children and adults

Clinical criteria for diagnosis of PWS based on phenotypic features were published in 1993 by Holm et al. [14]. The original checklist of signs and symptoms has been revised over the years and remains useful for clinicians [15]. Nowadays, though, the confirmation of the diagnosis always requires the implementation of molecular genetic testing.

Typical dysmorphic features of PWS are as follows: narrow face, narrow bi-frontal diameter, almond shaped eyes, small lips with thin upper lip, small hands and feet, and short stature. Hypopigmentation of hair, eyes, and skin is also characteristic [15, 16].

There are age-related differences in clinical manifestation of PWS. In infancy, hypotonia and feeding difficulties due to poor muscle tone affecting sucking reflex are typical. Nowadays PWS is most commonly identified at this stage; clinical criteria should always be supported by genetic testing before the final diagnosis is established [17, 18]. In some cases, though, the diagnosis is made at a later age (even in late adolescence or early adulthood). Symptoms that may suggest PWS and require further examination are presented in Table I.

Many of the clinical manifestations of PWS, such as insatiable appetite leading to obesity, decreased growth rate, hypogonadism, thermoregulatory abnormalities, increased pain threshold, and impaired gag reflex, are linked to hypothalamic and pituitary dysfunction [3, 20].

Table I. *Features and symptoms suggestive of PWS [3, 15, 19]*

Neonates and infants	
• hypotonia	
• feeding problems and failure to thrive	
• weak cry and decreased activity level	
• delayed psychomotor development	
• hypogonadism	
Children	
2–4 y.o.	• more prominent psychomotor delay
	• decreased growth rate
	• rapid weight gain
	• excessive appetite
6–12 y.o.	• persistent hypotonia (in the majority of patients)
	• complete lack of satiety
	• developing of central obesity
	• intellectual disability (in most patients)
	• hypogonadism
Adolescence (in both sexes)	
• delayed or absent puberty	
• short stature	
• increasing obesity	
• ventilatory disorders (especially sleep-related)	
• spinal deformities (scoliosis)	
• behavioural disorders (may become more prominent at this age)	
Adulthood	
• obesity and its complications	
• short stature	
• intellectual disability	
• behavioural disorders	
• hypogonadism	
• characteristic dysmorphic features (small hands and feet, facial appearance)	
• patient history includes infantile hypotonia and behavioural disorders in childhood.	

PWS genotype and phenotype

Individual phenotypical traits have not yet been precisely mapped onto specific genetic defects underlying PWS. However, certain phenotypical differences between patients with PWS due to deletion 15q and uniparental disomy 15, including the frequency and/or severity of some of the symptoms, have been observed. Patients with 15q11–q13 deletion:

— present with more typical phenotypic symptoms of PWS, such as the characteristic facial appearance, hypopigmentation of hair, eyes, and skin;
— show higher incidence of behavioural disorders, sleep disorders, paresis, and speech articulation disorders [21];
— in people with slightly larger deletions (type 1), stereotypical behaviours are more severe; these patients also exhibit lower intellectual and adaptive skills in comparison to patients with type 2 deletion [22, 23].

Patients with uniparental disomy (UPD):

— may not present with typical dysmorphic features (facial appearance, hypopigmentation), which may lead to a later diagnosis [3, 23];
— are less skilled at jigsaw puzzles (which is characteristic for PWS patients);
— have higher verbal IQ and less disruptive behavioural profile [24];
— more frequently exhibit autistic spectrum disorder features [24];
— have an increased risk of psychosis [22].

PWS behavioural characteristics

The presence of numerous severe behavioural disorders is characteristic for PWS patients. These include: lack of mental flexibility and stereotypical behaviour, strong resistance to change of introduced routines, deficits in social cognition and skills, compulsive behaviours and perseverations, as well as sudden temper tantrums [18, 19].

The degree of intellectual disability in PWS patients varies widely, ranging from profound through moderate to mild, with 27% of patients scoring within the borderline and a further 5% having average IQ (Table II). Regardless of the degree of intellectual disability, social skills in all PWS patients are far from adequate for age or even IQ score; therefore, patients are not able to function independently, requiring constant care and supervision of dedicated carers [25, 26].

Many behavioural traits present in PWS are similar to autistic spectrum disorder (ASD). The available data indicate that ASD may in fact affect up to 19% of patients with PWS [26]. Patients with maternal disomy and type 1 deletion are at particularly high risk of developing autism [27].

It has been noted that behavioural disorders in PWS, as well as their severity, seem to be related to age and BMI, especially in adolescence [28]. They also appear to become milder in older adults [29]. Psychotic episodes are observed in 10–20% of young PWS patients [30].

Multidisciplinary comprehensive care for adult patients with PWS

As in paediatric practice, a comprehensive multidisciplinary care model is key to effective management of PWS in adult patients [3, 15]. Until the 1990s, the available therapeutic measures were limited to low-calorie diet and physiotherapy. All too often, these instruments did

Table II. *IQ ranges in PWS [25]*

IQ	%
Average	5
Borderline (70–85)	27
Mild intellectual disability (55–69)	34
Moderate intellectual disability (40–54)	27
Severe to profound intellectual disability (< 40)	6

not suffice in prevention of the development of morbid obesity, despite the high engagement of both carers and doctors. However, over the last 20 years major advances have been made in medical care management of both children and adults with PWS [18]. These are summarised in Table III.

Treatment of adult patients with PWS

In adult care settings, the aims of treatment of PWS patients include:
— prevention of the development of obesity and associated comorbidities — the main objective;
— early diagnosis and treatment of metabolic complications;
— treatment of hormonal disorders;
— mental health stabilisation;
— nutritional guidance and adequate dietary management;
— on-going physiotherapy (scoliosis);
— early diagnosis and treatment of other complications in adults with PWS (e.g. obstructive sleep apnoea).

To prevent the development of obesity and metabolic complications, it is recommended that:
— dietary regime be maintained (including properly balanced meals with reduced caloric content of ca. 1000 kcal per day);
— physiotherapy programme be continued (as well as regular physical exercise);
— rhGH therapy be continued in patients meeting the clinical criteria;
— diagnosis and treatment of hypogonadism be put in place.

Table III. *The required engagement of different medical specialities and the most common challenges encountered in care and treatment of adult PWS patients [3]*

Medical speciality	Diagnostic and treatment areas
Endocrinology	human recombinant growth hormone treatment
	hypogonadism
	hypothyroidism
	adrenal insufficiency
	obesity
	osteoporosis
Diabetology	insulin resistance
	type 2 diabetes
Orthopaedics/ /physiotherapy	scoliosis
	preventive, curative, and rehabilitative physiotherapy
Pulmonology	obstructive sleep apnoea
	respiratory infections
Laryngology	hypertrophy of palatine tonsils
Cardiology	dyslipidaemia
	hypertension
Gastroenterology	constipation
	gastroesophageal reflux disease
	hernia
Nutrition Specialist	maintenance of a balanced low-calorie diet
Psychiatry/ /Psychology	behavioural disorders
	psychosis
	adaptive disorders
Stomatology	thick saliva, resulting in caries
	enamel hypoplasia
Urology	cryptorchidism
	phimosis
Gynaecology	gynaecological monitoring during hormone replacement therapy
	reproductive health
Dermatology	skin picking
Anaesthesiology	problems with intubation and ventilation (resulting from specific craniofacial features and reduced mobility of the cervical spine)
	altered/paradoxical reactions to standard doses of anaesthetics

Growth hormone deficiency

Short stature is a prominent feature of patients with PWS. It is the result of GH secretion disorders, which include decreased spontaneous GH secretion, pathologically decreased response in GH stimulation tests, as well as reduced secretion of IGF-I [31].

The first attempts to treat PWS with rhGH preparations date back to the 1970s and 1980s. At that time, its beneficial effects were shown not only to increase the rate of growth, but also to improve the bodily composition [9, 32].

Since the 1990s, growth hormone treatment has been integrated into the comprehensive care for patients with PWS in a growing number of countries. In Poland, children with PWS have been treated with rhGH since 2006 within the framework of the dedicated Therapeutic Health Programme, financed by the National Health Fund. In 2016 rhGH therapy

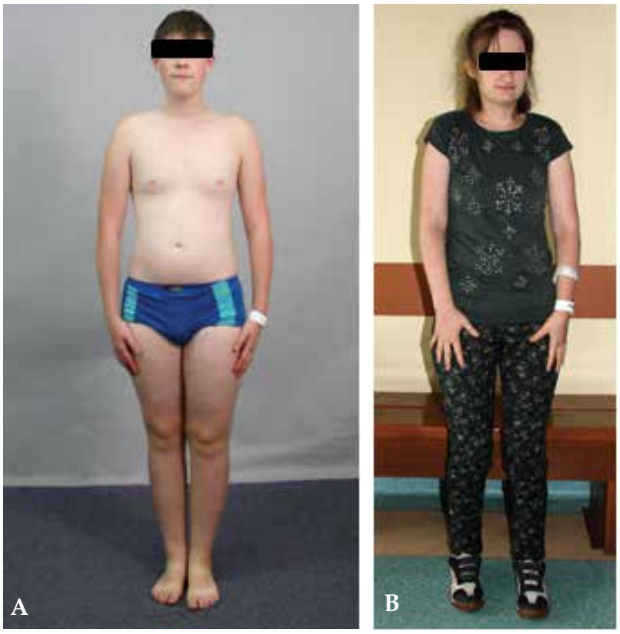

Figure 1. A. *Adult patient with PWS (19 y.o.) — height 176 cm, BMI 24 kg/m²*. **B.** *Adult patient with PWS (26 y.o.) — height 163 cm, BMI 22 kg/m². Both patients received rhGH therapy in paediatric centres and have been transitioned to adult care, where the treatment and comprehensive care are continued*

Figure 2. *Adult patient with PWS (20 y.o.) — height 155 cm, BMI 39 kg/m², never treated with rhGH*

was extended to include adult patients continuing the therapy [1, 3, 7, 8]. The list of treatment centres is available on the website of the Ministry of Health (http://www.mz.gov.pl) [1].

In childhood and adolescence rhGH therapy in PWS serves two primary goals. The first is to achieve a final height within the normal range for a given population, while the second is to compensate for metabolic disorders caused by absolute or relative GH deficiency [33]. Given the proven metabolic benefits of GH therapy, it is very important to continue treatment in adults with PWS. It also helps to protect patients with PWS from the psychological consequences of significant growth deficiency and morbid obesity [3, 33–36] (Figure 1A, B). Short stature, even if not always prominent in early childhood, almost always becomes an issue in the second decade of life in untreated PWS patients. Historically, in the absence of rhGH treatment, the mean body height was 155 cm for men and 148 cm for women (Figure 2). The size of hands and feet was also below average in untreated PWS patients (the average length of the adult male foot was 22.3 cm, while the adult female foot was 20.3 cm) [37].

Growth hormone serves different functions in different developmental stages [38]. During the growth period, it stimulates linear growth and influences bone mineralisation. Due to its anabolic effect, it also increases muscle mass and strength. Through its role in lipolysis regulation, GH reduces the percentage of fat in the body composition, lowers the level of total cholesterol, LDL cholesterol, and triglycerides, and increases the concentration of HDL cholesterol [20, 32, 39]. In patients with PWS, treatment with rhGH is also aimed at improving ventilation and the breathing pattern, which may reduce the risk of sleep apnoea and its consequences, including death. In addition, because of increased resting energy expenditure, a higher level of physical activity becomes attainable, which facilitates the course of physiotherapy as well as the maintenance of nutritional status. Both are key factors in the management of patients with PWS. In cases of PWS, the procedure of choice is to start GH therapy as early as possible. Often the treatment is introduced in the first months of a child's life, once the diagnosis has been genetically confirmed [1, 28, 39, 40]. GH therapy has a positive effect on improving muscle strength and tone, which translates into better effects of early physiotherapeutic intervention. Patients with genetically confirmed diagnosis of PWS are qualified for GH therapy by the Coordination Team for Growth Hormone Application. According to the rules of the Program "Treatment of Prader-Willi Syndrome" [41], patients with BMI below 97th percentile for sex and age, with documented systematic adherence to low calorie diet and participation in physiotherapy, are eligible for GH therapy. A six-month observation period at a reference centre providing rhGH therapy is also obligatory [1, 41]. It seems that this requirement is not justified in infants and small children who have not developed

obesity. The appropriate modification should be included in the text of the Therapeutic Program.

Treatment with rhGH is contraindicated in people with an active proliferative disease, as well as in patients with symptoms of intracranial hypertension. The medication is administered by subcutaneous injections, one dose every evening, with the help of a dedicated pen. As stated in the Therapeutic Program, patients under 18 years of age are eligible for rhGH treatment, while in adults rhGH therapy is currently only carried out as a continuation of treatment initiated in childhood. It has been demonstrated that the effective dose of rhGH in patients with PWS, which allows both the desired growth increase and metabolic effect in children, is 0.18–0.47 mg/kg/wk. [1]. Following the sudden deaths of patients undergoing GH therapy, which most often occurred during the first nine months of treatment [3, 12, 40], the current recommendation is to start treatment with lower doses (e.g. 0.009–0.012 mg/kg/day), and increase them gradually, while monitoring for IGF-I levels and clinical symptoms (this recommendation is not yet included in the Therapeutic Programme for PWS).

The metabolic and physiological demands for growth hormone are significantly lower in adulthood; hence the required dose amounts to ca. 30–50% of the dose used in the paediatric population. If treatment with rhGH is initiated in an adult PWS patient, the initial dose of 0.1–0.2 mg/day is recommended [3], which may be gradually increased to a maximum of 1.6 mg/day. Monitoring of the clinical condition of the patient is required, especially for the concentration of IGF-I, which should ideally remain within the upper range of the reference range [42]. These recommendations should be reflected in the provisions of the Therapeutic Programme. Following discontinuation of GH therapy in adult patients with PWS, obesity development and changes in body composition have been observed, with a decrease of muscle mass and increase of adipose tissue. Laboratory tests indicated a decrease of IGF-I and HDL-cholesterol levels after GH therapy cessation [39, 43–45].

Treatment monitoring

In all PWS patients treated with rhGH, monitoring of IGF-I and IGFBP-3 concentrations is strongly recommended. Additionally, all patients should undergo carbohydrate metabolism evaluation tests before the onset of treatment and during its course [1] (Table IV).

People with PWS may have breathing difficulties while sleeping, both central and peripheral in nature. Breathing disorders of the peripheral type may result from such factors as obesity, the presence of thick, sticky saliva, spinal deformities, tonsil hypertrophy, narrow airways, or a combination of some of the above symptoms. The impact of rhGH treatment on respiratory disorders has been repeatedly evaluated [43, 46, 47]. An improvement in ventilation was reported in some patients, probably resulting from the improvement of muscle strength; at the same time, however, other patients experienced an increase in the number of obstructive sleep apnoea events, particularly during respiratory tract infections and/or when tonsil hypertrophy was present. Therefore, the recommendations regarding GH therapy in patients with PWS advise conducting a periodic polysomnography test as well as regular laryngological consultations assessing the upper respiratory tract patency [1, 3, 12].

During the growth period all patients with PWS receiving GH therapy should be monitored for the development and/or progression of scoliosis. Continuous orthopaedic and physiotherapeutic assessment is recommended. However, scoliosis as such is not typically an indication for discontinuation of rhGH treatment [9, 48].

Growth hormone also reduces plasma cortisol levels by increasing the activity of 11-beta hydroxysteroid dehydrogenase type 2, which may lead to unfavourable consequences in PWS patients. Therefore, the adrenal cortex function should be evaluated before the start of rhGH therapy [49].

Treatment of obesity

Prevention of the development of obesity is of utmost importance in this group of patients. PWS is the most common cause of genetically determined obesity. Unceasing lack of satiety and increased appetite become manifest in these patients during the second year of life and persist throughout childhood and adolescence, when the symptoms usually become more severe.

However, in a few adult patients with PWS appetite stabilisation has been observed. Whether this phenomenon is related to certain acquired eating habits accompanied by strict environmental control or is the result of age-related processes in the neurohormonal system is not yet known [50–52]. Because treatment of PWS-related obesity with currently available pharmacological agents has not been effective [53–56], the procedure of choice is the strict implementation of a reduced-calorie diet (1000–1400 kcal) and regular physical exercise.

Bariatric operations are not recommended in PWS because they do not affect the sense of satiety; because they do not effectively limit the intake of meals, the incidence of complications is high [57].

Treatment of hypogonadism

Hypogonadism is observed in both sexes and every patient with PWS requires appropriate diagnostics in this respect. Most often, hypogonadism is of central origin

Table IV. *Diagnostic tests and consultations required under the Therapeutic Programme [1]*

Assessment before qualification for treatment	
• diagnosis of the Prader-Willi syndrome, based on clinical features, confirmed by genetic testing • IGF-I concentration test • assessment of bone age (required bone age: under 16 years in girls and under 18 years in boys) • nutritional status assessment, measured by BMI, (required BMI: below 97th percentile for sex and age) • assessment of glycaemia, required oral glucose tolerance test (OGTT) with measurement of glycemia and insulinaemia • laryngological consultation, due to the risk of occurrence of worsening of sleep apnoea	
Treatment monitoring	
After 30 days	• laryngological consultation
After 90 days	• IGF concentration test, follow-up IGF-I concentration tests administered every 90 days until the optimal rhGH dose is determined, then – once a year • laryngological consultation, follow-up depending on clinical symptoms
Every 90 days	• nutritional consultation • physiotherapy consultation
Every180 days	• blood glucose concentration test • TSH concentration test • FT4 concentration test • electrolytes concentration test
Every 365 days	• nutritional consultation • physiotherapy consultation • gynaecology consultation (applies to girls over 10 years old, girls under 10 years old — if needed) • cardiology consultation, echocardiography for patients with cardiovascular diseases • psychological consultation with an assessment of intellectual development (in children aged 7 years and older) • assessment of psychomotor development (in children under 7 years of age) • lipidogram (total cholesterol, LDL, HDL, triglycerides) • glycated haemoglobin (HbA1C) • oral glucose tolerance test (OGTT) with measurement of glycaemia and insulinaemia • IGF-I concentration • X-ray of hand and wrist with proximal forearm bone (for assessment of bone age, the test should not be performed in patients continuing treatment after reaching the bone age of 18 years) • in patients with delayed puberty — stimulation test of gonadotrophin secretion (if required) • nephrology and urology consultation — in the case of recurrent urinary tract infections or congenital malformations of the urinary tract: abdominal ultrasound, urinalysis, and urine culture test • orthopaedic consultation — if femoral head exfoliation is suspected: diagnostic imaging tests (X-ray, ultrasound, CT, MRI) • neurology and ophthalmology consultation — in the case of symptoms suggestive of CNS tumour (pseudo-tumour cerebri): CNS imaging tests (CT, MRI)
Exclusion criteria	
• lack of cooperation with the patient or carers; discontinuation of systematic rehabilitation or dietary treatment • increasing obesity, despite the implementation of comprehensive therapy including growth hormone treatment, nutrition management, and physiotherapy (increase of BMI by 2 standard deviations or more measured in relation to population standards adjusted for age and sex) • onset or worsening of nocturnal apnoea • ongoing diabetes or diabetes onset during GH therapy	

(hypogonadotropic hypogonadism). However, in some patients, usually male, primary hypogonadism (hypergonadotropic hypogonadism) may be present [58]. The clinical picture of men with PWS includes *micropenis*, small, and hypoplastic testes, with reduced pigmentation of the scrotal skin. More than 80% of boys are diagnosed with cryptorchidism [59, 60]. In females hypoplasia of the labia and clitoris is observed, as well as the primary

amenorrhoea (about 54%). If present, menarche usually occurs after the age of 15 years. Therefore, it is recommended that hormone replacement therapy (HRT) be initiated in adolescence, which should be continued in adults. Intellectual disability should not be a reason for HRT delay in such cases. There is no explicitly defined treatment regimen for adult patients. In women, it seems more convenient to use an HRT transdermal patch, which is well tolerated and does not affect the metabolism of rhGH in the liver. In boys, testosterone treatment should be started with a low dose ($^1/_3$ to ½ of the recommended dose for adult men, e.g. 50 mg *i.m.* every 2 weeks) and then gradually increased. Testosterone administered intramuscularly is preferred. The transdermal and gel preparations, due to the habits of patients with PWS (skin picking), are less frequently used.

In patients receiving testosterone supplementation, aggressive behaviour and agitation are not observed. The inclusion and continuation of HRT in adulthood has a positive effect on the increase of bone mineral density and muscle mass, as well as on emotional and psychological development, because patients with PWS receiving HRT do not differ in physical development from their peers [60, 61].

Intellectual disability makes some of the patients (especially girls) more likely to become victims of sexual abuse. Both carers and schools should be informed of this danger.

A few cases of pregnancy in patients with PWS have been described in the literature [62, 63]. Taking into account the emotional and social immaturity and the risk of having a child with Angelman syndrome (which is caused by a deletion of 15q11–q13 region on maternally derived chromosome, less often by paternal disomy of chromosome 15 or imprinting errors), introduction of contraceptives is recommended. Both patients and carers can benefit from sexual and reproductive health consultation.

Patients with PWS, due to the coexisting deficiency of growth hormone and sex hormones, suffer from reduced bone mineral density (BMD), which increases the risk of osteoporosis and leads to reduced muscle performance and elevated bone turnover markers [64, 65]. As a result, there is an increased risk of fractures of both long and short bones [3]. There are no unanimous guidelines for management of osteoporosis in adult patients with PWS. The regime usually encompasses HRT, and calcium and vitamin D3 supplementation if necessary. Densitometry tests are also indicated.

Thyroid

Hypothyroidism in patients with PWS may be central or peripheral. Its prevalence in PWS is not clear; some studies estimate it at 20–30%, while others at 2.1%, which is a populational rate [3, 5, 66]. All children are screened for congenital primary hypothyroidism immediately after birth (TSH levels). Considering the possibility of manifestation of symptoms or onset of hypothyroidism (both primary or central) also later in life, it is recommended to determine the concentrations of TSH and free thyroid hormones (FT3 and FT4) soon after establishing PWS diagnosis, and then, to control them periodically during rhGH therapy (approximately every 6 months). Thyroid function should also be monitored in young adults when the doses of rhGH are reduced. If hypothyroidism is diagnosed, supplemental treatment with L-thyroxine is implemented in accordance with generally accepted guidelines [3, 67].

Adrenal glands

Patients with PWS are at increased risk of secondary adrenal insufficiency. Initially it was claimed that it may affect up to 60% of the PWS population [68]. However, subsequent studies relying on alternative methods of adrenal function evaluation (ACTH test) did not confirm such a high rate of adrenal insufficiency in PWS [69, 70].

It has been shown that the initiation of rhGH therapy may induce adrenal crisis in patients with early (subclinical) adrenocortical insufficiency. This is associated with the acceleration of peripheral metabolism of cortisol, which may explain the relationship between the increased rate of sudden deaths at the onset of rhGH treatment in patients with PWS and adrenal insufficiency [49, 71, 72]. For this reason, the morning serum cortisol level should be determined before starting PWS treatment with rhGH, as in the case of patients in whom L-thyroxine treatment is necessary.

The actual prevalence of adrenal insufficiency in patients with PWS remains undetermined. Consensus has not yet been reached among endocrinologists regarding the indications for supplementary treatment of functional central adrenal insufficiency [3, 15]. Administration of an auxiliary dose of hydrocortisone may be worth considering when the patient is under severe stress (e.g. surgery) and the suspicion of adrenal insufficiency is well-grounded in clinical history. Patients and caregivers should also be informed about the symptoms of adrenal insufficiency and proper reaction in case of its occurrence, bearing in mind that the manifestation of the symptoms may not be as pronounced, for example due to the elevated pain threshold and weakness of gag reflex [3, 6].

Disorders of carbohydrate metabolism

Disorders of carbohydrate metabolism in PWS may result from the appetite disorder and subsequent obesity

on the one hand and complications of rhGH treatment on the other. Insulin resistance pays a key role in the pathogenesis of diabetes. Historically, diabetes affected as many as 25% of adult PWS patients (especially those with morbid obesity) [6, 27]. The average age of its onset was 20 years. It seems, however, that over the last 15 years the incidence of carbohydrate disorders among people with PWS has fallen. This change can be attributed to better weight management attained thanks to earlier diagnosis, rising parental awareness, and growth hormone therapy.

In some adolescents, during puberty, abnormal fasting glucose levels and glucose intolerance are observed [3, 15]. Treatment with metformin is well tolerated and effective.

Behavioural disorder management

Behavioural disorders affect PWS patients of all ages. Their presentation may be worsened by verbal communication difficulties. In PWS, speech and articulation disorders often have a complex aetiology (craniofacial abnormalities, thick saliva, various degrees of intellectual disability, autistic spectrum disorders). Continuous psychological care and speech therapy are recommended in children and adults [18].

Learning difficulties are common even in children with IQ within the normal range. Students with PWS thus require support in schools. Placement in integrated or inclusive settings is often the option of choice in the case of higher functioning children. Participation in occupational therapy workshops that help develop social skills is very beneficial.

Carers and teachers who interact with persons with PWS should possess thorough knowledge about the neurobehavioural profile of the condition.

There are no explicit guidelines on medications that could be recommended for the treatment of behavioural disorders in PWS, although serotonin reuptake inhibitors (SSRIs) appear to be beneficial in some cases, especially in the management of obsessive-compulsive disorders in adolescents and adults with PWS [73].

Conclusions

A comprehensive care model is the basis for effective treatment of PWS patients. It should encompass appropriate dietary management, support for the environment (family, friends, school), and comprehensive, multi-disciplinary medical care.

While the goals and guidelines for paediatric care have been established in recent years, in the case of adult PWS patients there is only limited knowledge based on experience with a small number of relatively young patients. Preliminary observations, however, suffice to define the range of specialist care and interventions that should be offered in reference centres for PWS adults. Proper care over this population requires close cooperation between many professionals representing many specialities: endocrinology, diabetology, gynaecology, andrology, urology, psychology, psychiatry, nutrition science, orthopaedics, and laryngology (Table V).

Only such complex care provides a chance for patients with this serious, genetically determined condition not only to achieve the average length of life, but also to attain higher quality of life.

Table V. *Main recommendations for management of patients with PWS*

Early diagnosis based on clinical criteria and confirmed through genetic testing makes it possible to introduce proper clinical management as early as possible (even in infancy)
Close cooperation is needed between paediatricians and adult care specialists during the transition period of patients who have attained majority to adult care reference centres that provide multidisciplinary treatment
Support and education provided for family and carers is central to PWS management
Institution and constant monitoring of appropriate eating patterns, food access control, and regular physical exercise are indispensable elements of obesity prevention
Starting rhGH therapy in early childhood and its continuation in adulthood provides optimal treatment outcomes in PWS
There is a need to establish PWS residential supported living homes, where adult PWS patients could stay under the care of qualified caregivers (including a psychologist, nutrition specialist, and physiotherapist)

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