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PRADER WILLY'S SYNDROME DIAGNOSED IN EXTREMELY OBESE FEMALE ADOLESCENT

Introduction: Nutritional obesity is the most common cause of obesity (95%) in childhood and adolescence. Morbid obesity (5%), which usually begins at an early age, can be caused by monogenic disorders, various genetic syndromes, endocrine diseases-disorders, central nervous system lesions or iatrogenic causes.

Presentation of the patient: A female adolescent aged 13 is presented who was due to obesity referred to the Center for the Prevention and Treatment of Obesity in children and adolescents at the Special Hospital "Cigota" at Mt. Zlatibor. Low height/stature and dysmorphic features: a face with a narrow bifrontal diameter, almond-shaped eyes, strabismus, small hands and feet, delay in puberty development and lagging in psychomotor development have indicated the morbid obesity. Anamnestic data on hypotonia and difficulty in feeding, psychomotor lagging behind, obesity since the third year of age, triggered a suspicion of Prader Willy's syndrome. The suspicion of this syndrome was confirmed by a molecular DNA analysis which indicated a deletion on the long arm 15q11.2.

Conclusion: Obesity, endocrinolopathies, retardation in psychomotor development and behavioral disorders in people with Prader Willy's syndrome require a complex multidisciplinary treatment. Early diagnosis and adequate treatment prevent the occurrence of complications and improve the quality and length of life of the patients.

Key words: obesity, Prader Willy's syndrome, growth hormone

INTRODUCTION

Nutritional obesity is the most common cause of obesity (95%) in childhood and adolescence. It is important to distinguish the primary, i.e. exogenous or nutritional obesity from rare forms of secondary obesity caused by genetic disorders, endocrine

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diseases, central nervous system lesions, or iatrogenic causes. With the increase of obesity in children and adolescents, it is increasingly important to identify children with secondary obesity as early as possible. Prader Willy's syndrome is the most common cause of genetic obesity. Through the case study, the aim of this paper is to point out the importance of a timely diagnostic and therapeutic approach in a patient diagnosed with Prader-Willy's syndrome.

PRESENTATION OF THE PATIENT:

I. B is a patient who was admitted at the Center for Prevention and Treatment of Obesity in Children and Adolescents at the Special Hospital "Cigota" at Mt. Zlatibor at the age of 12 years and 10 months. The patient is obese by a general type, with the body mass of 66. 4 kg, BMI 32.5 kg/m² (> p97, 2.95 SD), waist size of 96.00 cm (> p95), and low body height (short stature) of 143.00 cm (p3.3, -1.84 SD) (Graphs 1 and 2). According to the mother, the girl has been obese since the age of three, she has a hypercaloric diet and hyperphagia. She does a recreational swimming training. She has not established a menstruation. She attends the sixth grade of primary school and achieves poor results (2). She distinguishes odors, has not had any head injuries, nor brain inflammation.

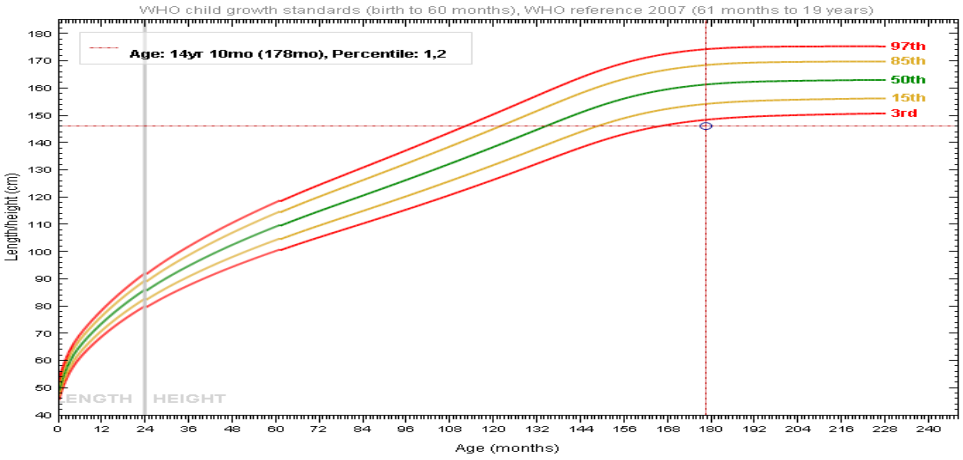
From a personal history: she is the second child from the second controlled pregnancy, the labor was in due time and of a regular flow, in a natural way. Body mass at birth was 2,950 g, height 52 cm, AS 9. After birth, she was hypotonic, she was breast fed with difficulty. She had natural nutrition until the second month, then fed with an adaptive milk formula. Controlled by a physiatrist and orthopedic surgeon, by the second year she had been wearing the Pavlich's apparatus due to the luxation of the hips. She started to walk after the second year. She began to speak after 3 years of age and because of a speech disorder, she was controlled by a speech therapist. Because of her poor speech, she started to go to school one year later than normal. Allergies so far have not been shown. She was vaccinated regularly for her age.

Family history: The body height of her father is 173.9 cm, of her mother is 167.8 cm, C height 164.3 cm (P50-75). The mother got the menstration at the age of 16, the elder sister is 18 years old, she is 166 cm tall. Her father's mother and mother's father are obese, and mother's mother and father's father have hypertension.

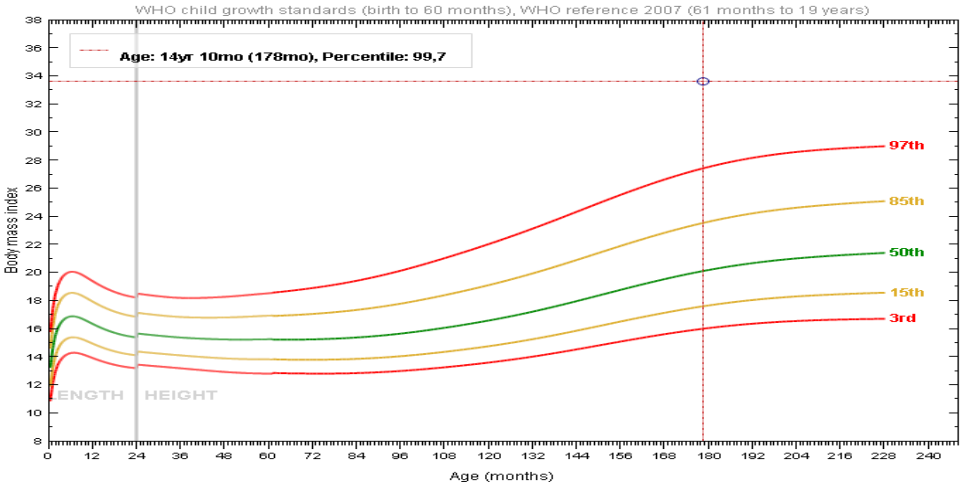
An objective examination has shown that there is an eumetabolic condition, an initial acanthosis on her neck, nacrous stretch marks on the breasts and hips. The teeth have been naturally changed, she has all teeth sixs, the dentition is irregular. A high shaped hard palate, low positioned earlobes, triangular lips. The thyroid gland is of the standard size and consistency, without palpable noduses. The finding related to the heart and lungs is normal, normotensive, liver and spleen are not palpable, there are

no edemas. Breasts are enlarged due to fatty tissue. Axial hairness A2. Small hands and feet. IV metacarpal bones of hands are short. External genitals are of a female type, P3. Neurological finding is normal.

Graph 1. Body height



Graph 2. ITM



The following additional diagnostic procedures were performed:

Laboratory analyses: negative inflammatory syndrome, without anemia, glycemia, lipidogram, hepatogram, electrolytes -referential values. Hormone analysis: Cortisol at 8 a.m. was 731 and at 6 p.m. it was 210 nmol / l, FSH 0.4 IJ / l, LH <0.14 IJ / l, prolactin 228 mLi / l, estradiol 6 pmol / l, TSH 3.1 mU / L, fT4 13.5 pmol/l.

Radiography of the left hand and low arm: Bone maturity corresponds to the age of a girl of about 12.5 years. Finding of a psychologist: Intellectual development is disharmonic, the overall functioning is in the Light Mental Illness Category IQT 68 (verbal IQ 82 Non-verbal IQ 58). Behavior and emotional development correspond to the younger age.

She was released on the 14th day, the body weight was decreased by 2.1 kg and the waist size by 4 cm. Due to anamnestic data, extreme obesity, low height and present stigmata which indicate to Prader Willy's syndrome, she was referred to a tertiary institution.

In two years, when she was 14 years and 11 months old, she was to check in for an examination again. According to the mother, she was not examined at the tertiary institution. Due to the low body height of 146.2 cm (below P3), extreme obesity, BMI of 32.3 kg/m², behavioral problems, hyperinsulinemia during OGTT and necessary genetic analysis, she was referred to a tertiary institution again. Post-hospitalization tests were done:

Ultrasonic examination of the abdomen: the finding was normal. The examination was done by an ophthalmologist: Strabismus. The examination was done by otorhynolaryngolost: the finding was normal. Molecular DNA analysis revealed the deletion characteristic of the Prader Willy's syndrome: 15q11.2 (P064-c). Due to secondary hypogonadism, she was referred to a gynecologist and after the examination and in agreement with the parents, the induction of puberty was started up. The colonidine test indicated a lack of growth hormone, but as she reached skeletal maturity (14.5 years), no growth hormone treatment was initiated. There are regular controls by an endocrinologist and gynecologist and the therapy: Metformin a 500 mg 1 + 0 + 1 tablets and estradiol.

DISCUSSION

Prader-Willy's syndrome was first described in 1887 by J. Langdon Down, but the syndrome remains unknown until 1956 when A. Prader, A. Lambhart and H.Willy published a presentation about nine people who show the same clinical characteristics (1). The syndrome is manifested with muscle hypotonicity at the age of infants, difficulty in feeding, a short stature, small hands and feet, hypogonadism and extremely expressed hyperphagia. Hyperphagia conditions the development of pathologic obesity, which is the main cause of diabetes type 2, which is in about 10% of patients diagnosed in the adolescent period. The children of short stature due to growth hormone deficiency, they are hypogonadal are mostly infertile, and they also might develop hypothyroidism and adrenal insufficiency. Most patients have cognitive dysfunction and developmental lag. Dysmorphic features in the clinical picture are present in most patients (2). The patients have a characteristic face with a narrow

bifrontal diameter, a thin upper lip and lowered angles of lips, almond-shaped eyes, sparse, thick saliva and hypoplastic look. About 60-70% of the diseased have strabismus and 40-80% have scoliosis (3).

The incidence of the disease in Europe is 1:30 000 live-born children. In about 65-70% of the patients, the syndrome is caused by deletion or structural disorder on the long arm of the chromosome 15q11-13 on the one that originates from the father. Another chromosomal disorder that causes this syndrome is the existence of two copies of the maternal chromosome 15 (*maternal uniparental disomy),* occurring in 25% of patients, and 5% of patients are with the disorder of methylation (4).

Due to hypotonia, a poor physical activity and decreased muscle mass, energy consumption is reduced, so changes in body composition in patients are present early, already at the infant age. Most of the children with Prader Willy's syndrome are late in psychomotor development (they sit only when they are 12 months old, they start to walk when they are 24 months old, after 36 months they adopt a dozen words). Intellectual lagging behind is becoming noticeable at the school age.(5).

In both genders, obesity is primarily central (6). In people with Prader Willy's syndrome, a lack of sense of satiety is dominant, the level of grelin is permanently elevated before the development of hyperphagia. Weight gain usually occurs between 2.1 and 4.5 years. Hyperphagia and further increase in body weight develop between 4.5 and 8 years and continue, with a loss of sense of satiety, and it comes to the onset of morbid obesity. If a diet is not controlled, the body mass of adolescents may be greater than 150 kg.

The clinical and diagnostic criteria presented by the numerical scale were used to diagnose this syndrome before the availability of a genetic analysis. (Table 1). The scale is easy for use and contains 6 large and 11 small criteria, of which each is valued 1 or 1/2 points. For the clinical diagnosis of this disease, 5 points are needed, of which 4 are from the gupe of large criteria for the age of up to three years. In older than three years, 8 points are needed, of which 5 from the group of large criteria (7).

Table 1. Diagnostic criteria for Prader Willy's syndrome

Large criteria (1 point)	Small criteria (2 points)
Neonatal/ hypotonic and poor breast feeding	Reduced fetal motility
Difficulties in feeding, no progress in development	Behavioral problems
Weight gain between the age of 1-6; obesity, hyperphagia	Apnea in sleep
Dysmorphic face features	Low stature
Hypoplasia of external genitalia, lack of or incomplete puberty	Lighter hair, eyes and tan in comparison to other family members

Lagging behind In u psychomotor development	Small hands and feet
	Narrow hands, flat border of ulna
	Strabismus, myopia
	Dense, viscose saliva
	Disorders in speech articulation
	Skin twitching

Clinical features and endocrinological disorders

Low stature/growth is often observed during early childhood. Low stature, obesity, body composition with dominant fatty tissue, low levels of insulin-like growth factor and poor growth hormone response in pharmacological stimulation tests, clearly indicate a growth hormone deficit (22). Low stature is caused by the absence of puberty rapid growth due to hypogonadism. Without a growth hormone therapy, the final height on average of men is 155 cm and women 148 cm (8).

People with Prader Willy's syndrome have hypogonadism, external genital hypoplasia, absent or late puberty and infertility. 80-90% of the patients have cryptorchism. Hypogonadism is a consequence of dysfunction of the hypothalamus, but also of primary damage to the gonads (9).

About 25% of the children with Prader Willy's syndrome have central hypothyroidism with low free thyroxine (fT4) and normal or lowered thyrotropic hormone (TSH). Dysfunction of the hypothalamus can lead to central insufficiency of adrenal glands and sudden death during acute illnesses. The incidence of adrenal gland insufficiency is 14-60%. Assessment of the adrenal gland function includes the determination of cortisol and ACTH at 8 a.m. The cortisol level > 500 nmol / l confirms the normal synthesis and excretion of cortisol. (10).

25% of the adult patients with PraderWilly's syndrome have diabetes of type 2.

Behavioral disorders are present in 70-90% of the people with this syndrome and are described as anger outbreaks, stubbornness, compulsive-obsessive behavior, and disorders from the autistic spectrum are often.

Dysfunction of the hypothalamus leads to the formation of central apnea and sleep disturbances. Obstructive sleep apnea results from obesity, tonsillitis hypertrophy and neuromuscular weakness. Polysomnographic recording should be done prior to the introduction of growth hormone therapy.

Dysfunction of the hypothalamus is caused by unstable temperatures, a high threshold for pain and inability to vomit. By that, a diagnosis of acute illnesses is made difficult. Particular caution is required in overeating which can lead to choking, dilatation of the stomach with necrosis and perforation. The death rate of the patients with PWS at the age of 6-56 years is 3% per year. The highest mortality is in children

up to 5 years of age, and the most common causes of death are respiratory inflammation and aspiration syndrome. In adolescence and adulthood, a high mortality rate is due mainly to complications caused by obesity (11). Breathing disorders during sleep, of a central or obstructive type, also contribute to sudden death.

Therapeutic possibilities

The treatment of patients with PWS requires a multidisciplinary team that includes a pediatrician, geneticist, endocrinologist, dietician, physiatrist, speech therapist, psychologist, psychiatrist, pulmologist and, if necessary, other subspecialists. The objective of the treatment is to prevent the onset of morbid obesity and comorbidity. The basis of treatment is a controlled balanced hypocaloric diet, substitution with a growth hormone with the addition of l-thyroxine, sexual hormones and glycocorticoids in case that their deficiency is developed. It is necessary to stimulate the psychomotor development of the patients and to treat complications.

From the moment of confirmation of the diagnosis, without waiting for the development of a typical clinical picture, it is important to plan a balanced diet. A quantity is important, but also a selection of foods that should have less energy values. From the age of infants to adults, the body mass and BMI should be maintained between the 25th and 75th percentile. Growth charts are used to assess the nutritional status for children with PWS. The timetable and the amount of meals must be planned, so it is necessary to provide 8 to 11 kcal per centimeter of the body height. Caloric intake may be higher in people who are on growth hormone therapy and if they are physically active for 30-60 minutes per day, and in adults up to 1800 kcal per day.

Hyperphagia is the main disorder of PWS and is present throughout the whole life. For now there is no pharmacological therapy, and there is no possibility of surgical treatment of this problem. Daily physical activity adapted to age and nutritional status increases muscle mass and strength, energy consumption and thus contributes to the control of the body mass.

Since early childhood, the assessment and monitoring of psychomotor development are important. Physical therapy is important for strengthening muscle tonus and strength, and in with speech-impaired patients, a speech therapy is needed.

The therapy with a growth hormone results in accelerating of growth, achieving the desired height, and the treatment results in a muscle mass increase, he increase of muscle strength and tonus, while increasing the physical activity and reducing fat tissue (12). The optimum time for the administration of growth hormone therapy is not defined, but according to the majority of authors, the therapy should be started prior to the onset of obesity, around the second year of life. The initial growth hormone dose is 0.5 mg / m^3/ day with a gradual increase of up to 1 mg / m^2 / day, as this dose provides a positive effect on the body composition.

In agreement with parents, puberty induction can be started at the age of about 12 years in girls and about 14 years in boys. The treatment leads to a gradual development of secondary sexual characteristics, an increase in muscle mass and bone mineralization, which results in the improvement of health and quality of life. In boys, the treatment begins with testosterone 50 mg intramuscularly every four weeks and the dose is gradually increased by 25-50 mg every six months. The dose for adults is 250 mg every two weeks. The dose of the medicine is harmonized with the patient's mood and behavior. It is desirable to apply the lowest dose that ensures clinical and biochemical eugonadism. For induction of puberty, girls are given 17β estradiol 0.25 mg / day orally or 14 μg / day transcutaneously with an adhesive plaster twice a week. Two years after the application of the estrogen therapy or after the establishment of menstrual bleedingin order to prevent endometrial hyperplasia, progesterone is added 200 mg / day orally, 10-14 days of the period (13).

The development of hypothyroidism is more common in early childhood, and the control of the thyroid gland function by determining fT4 and TSH should be started from the third month of life, despite the normal neonatal screening results. TSH controls are then to be repeated once a year, especially in the patients who are on growth hormone therapy. In case of development of hypothyroidism, levothyroxine therapy is introduced. Adrenal insufficiency needs to be diagnosed in time and the patients are to be treated with hydrocortisone. (Table 2).

TABLE 2. Treatment of patients with PWS

Balanced diet
Infants 0-12 months – normal growth, BM 25 – 75 percentile for PWS
When BM starts to grow, to introduce restrictions in diet- about 10 kcal / cm of body height
The total calorie intake consists of: 45% carbohydrates, 25% proteins and 30% fat
Physical activity – 30-60 minutes per day
Recombinant human growth hormone (rhHR) – initial therapy
0.5 mg / m^2, gradually to be increased to 1 mg / m2 subcutaneously in the evening
Induction of puberty
Boys aged about 14 (in agreement with parents) testosterone
Girls aged about 12 (in agreement with parents)
17β estradiol in tablets or transcutaneously, with the addition of progesterone
Hypothyroidism – substitution with l.thyroxine 1 – 2 μg / kg per day
Adrenal insufficiency – hydrocortisone substitution 10 mg / m^2 / day divided into three doses, in stressful situations a 2-3 times higher dose is given
Stimulation of psychomotor development – physical therapy, psychotherapy, exercises with a speech therapist

CONCLUSION

Extreme obesity, endocrinolopathies, lagging behind in psychomotor development, and behavioral disorders in people with Prader Willy's syndrome require a complex multidisciplinary treatment. Therapeutic options for the ill are limited, especially if the illness is diagnosed late. The example of our female patient, who was diagnosed at the age 15, confirms this. An early established diagnosis and an adequate treatment prevent the occurrence of complications and improve the quality and length of life of the patients.

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