Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.63, No.1(2023). p.51-6; DOI: 10.14238/pi63.1.2023.51-6

Case Report

A 14-year-old patient with Prader-Willi syndrome: a case report

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Prader-Willi Syndrome (PWS) is a disorder resulting from a loss of genetic information on chromosome 15q11.2-q13 inherited from the father. It can be caused by paternal deletions (65-75%) or uniparental maternal disomy (20-30%). The prevalence of PWS is estimated to be 1/10,000 - 1/20,000 births.[1] Although its incidence is relatively rare, PWS can cause major health problems for patients and decreased quality of life for their families.

The course of PWS is characterized by severe hypotonia in the neonatal period, severe feeding problems resulting in growth failure, as well as small hands and feet. Hypogonadism manifests as genital hypoplasia, delayed puberty, and infertility. Children with PWS have delayed motor and language development. Most patients have some degree of intellectual disability. Hyperphagia and obesity occur in early childhood. The patient's excessive eating behavior affects the patient's and family's quality of life, and is often responsible for high morbidity and mortality. **[Paediatr Indones. 2023;63:51-6; DOI: 10.14238/pi63.1.2023.51-6**].

Keywords: *case report; Prader-Willi syndrome; hyperphagia; complications; multidisciplinary management; outcome*

The most important complications of PWS affect the cardiovascular and respiratory systems and are induced by obesity. These complications are, in turn, directly responsible for the high mortality rates in children and adults with PWS. Cardiovascular complications may include hypertension, myocardial infarction, congestive heart failure, and stroke.

Early recognition and diagnosis of PWS is very important to prevent long-term complications, as early management is expected to improve quality of life. We report here on a child with PWS who was followed for 18 months to observe the direct course of PWS and implement optimal management with a multidisciplinary approach focused on preventing long-term complications.

We monitored the patient's diet, physical activity, linear growth, sexual development, nutritional status, early detection of complications, and quality of life for 18 months. The expected outcomes of optimal management are no long-term complications of obesity, no disturbances in sexual growth and development, and an increase in quality of life.

The case

A 14-year-old boy was diagnosed with PWS in December 2017. The clinical signs of PWS noted were obesity, very short stature, intellectual disabilities,

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Submitted February 8, 2021. Accepted February 28, 2023.

and delayed puberty. The patient was admitted to Dr. Sardjito Hospital, Yogyakarta due to a focal seizure in the hand in November 2017 (age 14 years). He also had hypertension, with a highest blood pressure of 180/100 mmHg. The hypertension was likely due to non-streptococcal acute glomerulonephritis (reddish urine, hematuria, proteinuria, negative anti-streptolysin titer O (ASTO), and normal complement level). Electroencephalography (EEG), brain CT scan, and echocardiography results were within normal limits. The patient was diagnosed with hypertensive encephalopathy due to hypertensive emergency caused by non-streptococcal acute glomerulonephritis. He received 5 mg/kg/day of phenytoin, 5 mg/day of amlodipine, and penicillin-class antibiotics. Phenytoin and amlodipine were given for 2 months, then discontinued after he became seizure-free and his hypertension was under control.

On December 4, 2017, the patient was admitted to the endocrine outpatient clinic for syndrome tracking. On physical examination, stage II hypertension was found (blood pressure 140/90 mmHg), and his anthropometric status showed a body weight of 54.5 kg, a height of 131 cm, and a body mass index (BMI) of 31.7 kg/m^2 (>+3SD). He was considered to have obesity and severe stunting. The boy's pubertal status was consistent with Tanner stage 1 (no pubic hair growth), micropenis (4 cm long), and his testicular volume according to orchidometer measurement was 8 mL. The boy was diagnosed with Prader-Willi syndrome based on clinical signs and physical examination findings: obesity, short stature, intellectual disabilities, and delayed puberty. Laboratory tests included blood glucose, HbA1C, and lipid profiles to track metabolic syndrome complications, with results within normal limits. Bone age examination results were appropriate for chronological age.

The patient was an only child and had no family history of PWS. He was born through a normal vaginal delivery assisted by a midwife. He cried immediately after birth and had no post-natal problems. He was able to run by 18 months of age, had no hypotrophic conditions or respiratory problems as an infant, and could talk by 2-2.5 years of age. At the time of this report, the boy was in 7th grade, attending a special needs school due to his learning difficulties. The boy was transferred to his current school after he had been bullied by classmates at a public school.

Growth assessment was done by measuring body height. At the start of monitoring (age 14 years 8 months), the child's body height was 133 cm, below the 3rd percentile based on the *American Academy of Pediatrics* (AAP) height curve for PWS children without growth hormone (GH) therapy. His body height increased to 140 cm at the end of follow-up (age 16 years and 8 days), but remained below the 3rd percentile of the height curve. The patient's body height was still very short compared to that of other PWS children.

BMI monitoring based on age for PWS children without GH therapy was shown in **Figure 1**. At the beginning of follow up, the patient's BMI was 30.52 kg/m2. By the end of the observation period, it had increased to 32.85 kg/m^2. When compared to normal children, BMI based on age was indeed above P97, or in the obesity range. However, the patient's BMI was still within the normal range between the P25 to P50 for PWS children.

Assessment of sexual development was done twice. On the first admission (14 years 2 months of age), the patient's pubertal status was Tanner stage T1 (no pubic hair growth), with micropenis (4 cm) and 3 mL testicular volume by orchidometer measurement. At the end of follow-up (16 years of age), he was at Tanner stage T3 (pubic hair to mons pubis, 10 mL testicular volume, and 5.5 cm penis length).

Complications of metabolic syndrome were monitored by measuring blood pressure, lipid profile, and blood sugar, with results within normal limits. There was no comorbid metabolic syndrome in the patient, although each parameter was not fully assessed. Echocardiography performed at the beginning of observation revealed good myocardial contractility and an ejection fraction of 79%. Doppler ultrasound of the carotid artery revealed no plaque or atherosclerosis in the right carotid artery and normal intima media thickness of 0.36-0.44 mm (**Figure 2**). There was no repeat episode of hypertensive complications until the end of the observation period.

The results of the Peds-QL examination were 59.7% at the beginning of the observation and 77.7% at the end of the observation. The patient's quality of life at the beginning of the observation was considered to be poor, as he had problems in the three main daily function domains, predominantly in physical

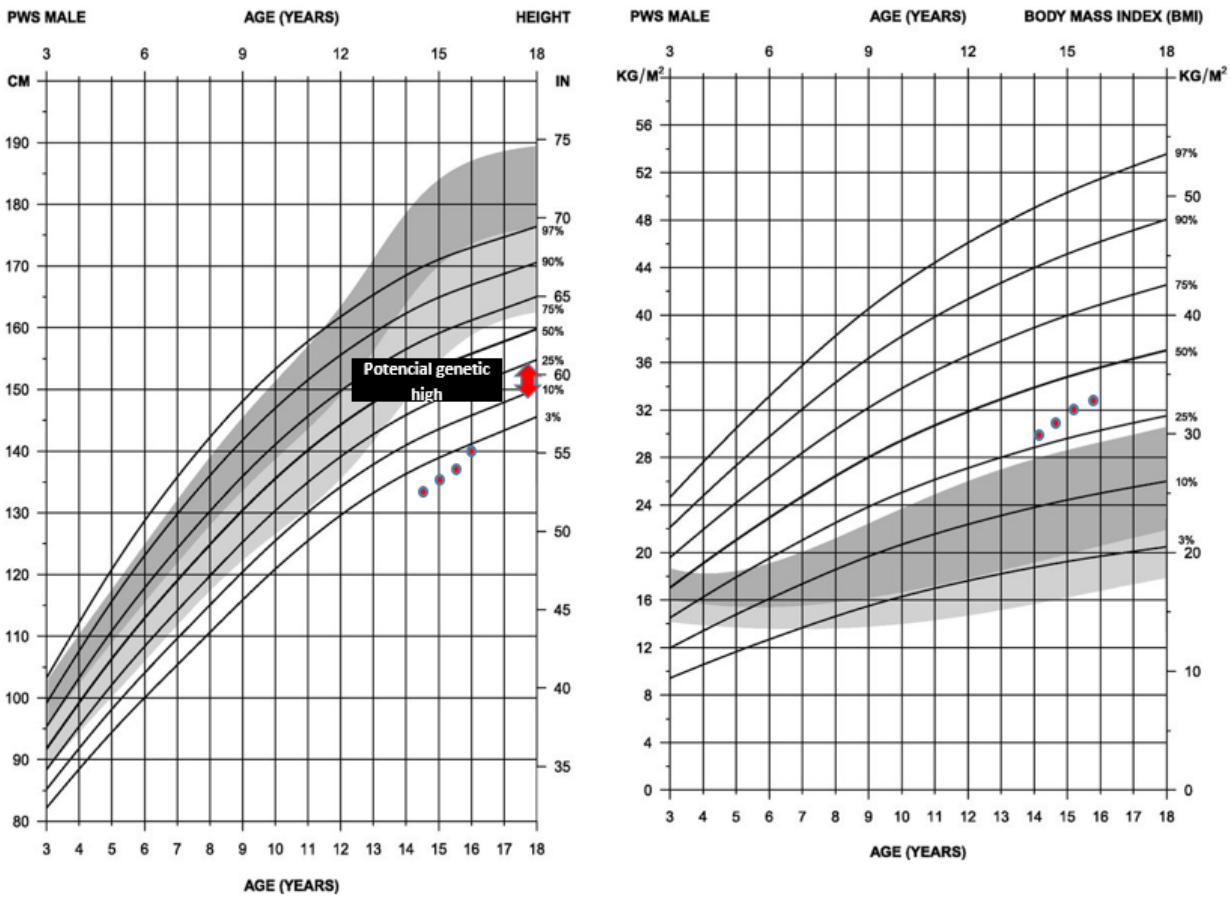

Figure 1. Growth and BMI monitoring with PWS-specific charts

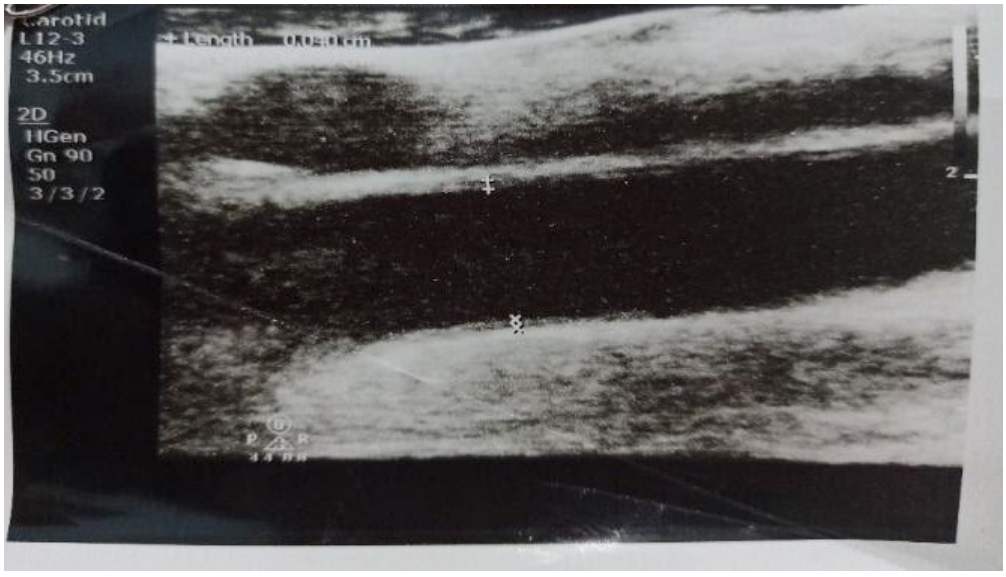

Figure 2. Doppler ultrasound of carotid artery

and emotional functions, followed by social function. Although the total score increased over the 18 months of observation, his quality of life remained poor, with a total score below 80 %.

Based on the patient's daily food recall diary, we estimated his daily calorie consumption to be 1,750-1,950 kcal per day. His total daily caloric requirement should have been 1,421 kcal/day, with a composition of 40% carbohydrates, 30% protein, and 30% fat. His diet was modified in the first three months of observation, with reduced food portions and increased physical activity. But the parents could not sustainably control the child's excessive appetite, leading to weight gain. During home visits, the parents were advised to reduce snacks and replace them with fruit. However, the patient did not like eating fruit. In addition, supervision and food control was so difficult that the program could not be properly maintained.

During the 18 months of monitoring, the patient engaged in physical activity around the house, bicycled in the afternoons at least three times a week for 30 minutes, watered plants every morning, and cleaned the house everyday. Yet, the intensity and duration of physical activity was still far below the expected target. For children aged 5-17 years, the WHO recommends moderate or vigorous physical activity for at least 60 minutes daily.[2]

In the present case, the parent's compliance was poor. In the first month of observation, the patient was not brought for the recommended visits to the endocrine, nutrition and metabolic disease, cardiology, and nephrology outpatient clinics. In the second month of monitoring, the patient refused to come to the hospital. Thus, in the third month of observation, interventions were done to address these problems in accordance with the recommendations for obesity management issued by the Nutrition and Metabolic Diseases Working Group of the *Indonesian Pediatric Society*.[3] These interventions included conducting home visits, taking regular anthropometric measurements, and checking cholesterol and blood sugar levels independently.

Discussion

Optimal management of PWS requires an interdisciplinary approach that focuses on anticipatory and preventive intervention and monitoring. Therefore, to prevent long-term complications, follow-up is required with contributions from various fields related to and involving medical care, nutritional counseling, behavior control, special education, and hormone replacement.[4]

Some evidence suggests that abnormal growth patterns, decreased lean mass, and increased fat mass are due to growth hormone (GH) deficiency. Children with PWS should have their linear growth monitored at least every 3 months. A subnormal linear growth rate is the first and most sensitive sign of growth failure. Linear growth failure in PWS children may indicate GH deficiency.[4] However, because GH deficiency is common in PWS, evaluation of GH deficiency is not always done before starting GH therapy. Growth failure is determined using the standard for children without PWS, and is defined as the downward deviation of height across two percentile curves, or a height velocity of <4 cm/year for pubertal children. Our patient's height velocity was 4.8 cm/year, so he did not meet the criteria for linear growth failure. Linear growth failure in children with PWS is an indication for recombinant GH therapy.[5]

The patient experienced delayed puberty which was characterized by the absence of secondary sex development at the age of 14 years. The profile of hypogonadism in PWS males has been well-documented. Clinical features include a small penis, scrotal hypoplasia, and cryptorchidism at birth, with spontaneous puberty followed by mid-pubertal arrest and reduced testicular volume attributable to a reduction in seminiferous tubules. Since hypogonadism is invariable in PWS, it is paradoxical that no clear treatment guidelines have been developed.[6]

Weight control remains the most important goal of any PWS treatment program. There is no recommended target for BMI reduction in PWS patients. In our patient, the BMI was kept between the P25 and P80 on PWS charts.[7] Control of obesity through dietary restriction is the cornerstone of effective management of PWS patients. However, controlling the weight of children with PWS is difficult if we apply the recommended RDA for normal children. To control obesity, caloric intake should be regulated below the requirement for normal children. Hence, the standard RDA balanced nutrition plan (60% carbohydrate, 15% protein, and 25% fat)

requires modification for PWS patients to 50-70% of the RDA for weight maintenance. A possible approach is to supply one-third of the calories from protein, two-fifths from carbohydrates, the rest from fat, and add vitamins and minerals. Providing adequate protein during caloric restriction will help maintain lean body mass.[8] Pharmacotherapy with anorectic agents such as phentermine and fenfluramine is not effective in controlling the appetite of PWS patients. Surgical therapy such as gastric bypass is also not recommended. In a retrospective review of PWS patients who underwent surgical treatment, 63% had only a low reduction in body weight.[9]

Obesity plays a role in the onset of metabolic syndrome in PWS patients, so weight control is the most important goal in the management of PWS patients. Metabolic syndrome in PWS is not directly treated with drugs, but by implementing a healthy diet and managing physical activity. If these interventions do not produce results, then statin administration should be considered in children over 10 years of age, although data on long-term effects are not yet available.[10] The LDL target is <130 mg/dL for children aged >10 years or a 50% reduction from baseline for children ages 8 to 10 years, especially for those with very high LDL levels.

Hypertension is one of the common comorbidities found in obese children. Based on a study in Italy on 109 children aged 2-18 years (50 obese, 59 not obese) with PWS accompanied by obesity, hypertension was found in 32% of obsese subjects, while in non-obese children the proportion of hypertension was 12%.[11] In our patient, glomerulonephritis was also thought to be the cause of acute hypertension and hypertensive encephalopathy in this patients. This is shown by the condition of hypertension which improved after the glomerulonephritis in the patient was resolved. Although monitoring blood pressure every two months shows normal results, weight control remains the most important goal in the management of patients.

PWS is not associated with renal complications. Several case reports of kidney problems in PWS patients include glomerulosclerosis, renal tubular acidosis, unilateral renal malmigration, and hydronephrosis combined with hydroureteral and vesicoureteral reflux. Some authors thought glomerulonephritis in PWS was associated with adaptive glomerular hemodynamic changes due to the extreme obesity.[12] In our case, glomerulonephritis may be associated with obesity, as there was no evidence of streptococcal infection in this patient.

Although our patient's total PedsQL score increased over the 18 months of monitoring, his quality of life was still categorized as poor, indicated by a total score of <80%. Similarly, a previous study reported that PWS patients often have a lower total PedsQL score than children without PWS. Therefore, education and motivation should be given to parents.

In summary, an 18-month observation and intervention was performed on a 14 year-old boy with Prader-Willi syndrome, obesity, intellectual disability, as well as history of stage II hypertension, hypertensive encephalopathy, and non-streptococcal acute glomerulonephritis. Holistic and comprehensive management measures of the patient's problems were carried out in accordance with the recommendations of obesity management based on the *Indonesian Pediatric Society*.[3]

Results of prospective patient observation showed that several targets were achieved. The BMI based on age was at P25-P80 of the PWS curve, there was no failure in linear growth and sexual development, and no complications of obesity. Blood glucose and cholesterol were monitored regularly during the 18-month period. Another successful target was the improvement of the patient's quality of life, although the quality of life was still categorized as poor.

The targets that were not achieved in this monitoring period were the application of the correct diet, incomplete monitoring of comorbid metabolic syndrome, failure in modifying behavior patterns to control hyperphagia, and avoiding a sedentary lifestyle. The patient was unable to reduce the food portions, snacks, or sugar consumption and his physical activities lacked intensity and duration.

Lack of family support and motivation was a contributing factor to the lack of management targets achieved. We hope that our patient will continue his commitment to a healthy lifestyle in order to experience further improvement in his quality of life.

Conflict of interest

None declared.

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