

A Case of Diabetes Mellitus in A Young Adult – An Unusual Presentation - Prader Willi Syndrome

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Abstract: *Prader-Willi syndrome (PWS) is the most common syndromic cause of human obesity and is associated with multiple endocrinopathies including type 2 diabetes mellitus (T2DM). Prader-Willi syndrome (PWS) is a multisystem complex genetic disorder, characterized by neonatal hypotonia, developmental delay, short stature, childhood obesity, hypogonadism, and characteristic facial features. With the rising prevalence of obesity and early onset T2DM in young adults, clinicians need to be aware of genetic syndromes associated with T2DM and obesity. We discuss a case of PWS which was diagnosed after evaluation of a male patient who presented to us with obesity and uncontrolled diabetes. Despite the presence of neurodevelopmental delay and suggestive syndromic features, the diagnosis in our patient was delayed because of lack of awareness about PWS.*

Keywords: Type 2 Diabetes mellitus (T2DM), obesity, Prader-Willi syndrome (PWS), Genomic imprinting

1. Introduction

Prader, Labhart, and Willi described the first patient with Prader Willi syndrome (PWS) in 1956. PWS is the most common syndromic cause of human obesity, with an estimated prevalence of about 1 in 25,000 births and a population prevalence of 1 in 50,000(1). It is caused by deficiency of one or more paternally expressed imprinted transcripts within chromosome 15q11-q13 and was the first recognized disorder related to genomic imprinting in humans(2). The phenotype is likely due to hypothalamic dysfunction, which is responsible for hyperphagia, temperature instability, high pain threshold, hypersomnia and multiple endocrine abnormalities including growth hormone and thyroid-stimulating hormone deficiencies, hypogonadism and central adrenal insufficiency. Obesity and its complications are the major causes of morbidity and mortality in PWS. Here, we discuss a patient, who presented to the Endocrinology out-patient department with uncontrolled hyperglycaemia, mental retardation and obesity and was found to have PWS on further evaluation.

2. Case Report

Our patient was a 23 year old male with subnormal intelligence brought by parents with complaints of obesity and uncontrolled blood glucose. He was born as second child of a non consanguineous marriage. His antenatal period was uneventful and was delivered post-term by lower segment caesarean section. His birth weight was 2.5 kg and had shrill cry after birth. There was difficulty in feeding him during infancy. There was global developmental delay

affecting gross motor, fine motor, language and social skills. He has an elder brother who is normal as is other children in their extended family. He has occasional temper tantrums. His scholastic performance was poor. From the age of 3 years, he started eating excessively and demanded food at frequent intervals with a history of increased weight gain thenceforth but was short compared to his peers. There was poor development of secondary sexual characteristics and external genitalia. He snores excessively while sleeping and has daytime sleepiness. There was history of fracture of both arms and gun stock deformity in right arm. He was diagnosed to have diabetes mellitus at 18 years of age on investigating for osmotic symptoms – polyuria, polyphagia and polydipsia and started on oral antidiabetic medications but had inadequate control.

Physical examination revealed a pulse rate of 80/minute and regular; blood pressure was 110/70 mm of Hg. His height was 147 cm (< 3rd centile, Height SDS = -4.3) with a target height of 168 cm (SDS= -0.34) and body weight of 80 kg (75-97 centile) with BMI of 37.02 kg/m². His height age was 12.5 years and bone age was 17 years. Waist circumference was 119 cm and hip circumference was 103 cm with Waist Hip Ratio of 1.15. Ratio of upper and lower segment was 1.12 and difference between arm span and height was 2 cm. He has narrow face with thin upper lips, downturned corners of mouth but his hands and feet are not small [figure 1]. He also has clubbing of fingers [figure 3]. He did not have goitre, purplish striae or polydactyly. He has gynaecomastia and thin reticular veins visible all over the body. He has no facial hair or axillary hair and has light coloured skin and iris. His voice is high pitched. He has

poor oral hygiene with caries tooth, gum hypertrophy and glossitis. External genitalia showed sparse pubic hair (P2), phimosis and balanoposthitis. Scrotum was pinkish, non-pigmented with bilateral testes palpable in scrotum. His stretched penile length was 4 cm (micropenis) (3) and testicular volume was 6 ml bilaterally with normal consistency [figure 2].

Cardiovascular, respiratory and abdominal examination was normal. Neurology examination, including dilated funduscopy was normal.

3. Investigations

The fasting and postprandial plasma glucose at presentation were 368mg/dl and 404mg/dl respectively while HbA1c was 15.8%. Lipid profile showed total cholesterol – 135 mg/dl, triglycerides – 267mg/dl, LDL-C-134mg/dl, HDL-C-45mg/dl. Liver function test, renal function test and complete haemogram were normal. Serum IGF1 was low at 45.3ng/ml (116-355 ng/ml), as was total testosterone at 25ng/dl [170-450]. LH was 1.41 mIU/ml and FSH was 4.07 mIU/ml indicating **hypogonadotropic hypogonadism**. Thyroid function, 8 am serum cortisol and plasma ACTH were within normal limits. Ultrasonography of abdomen, pelvis showed moderate fatty liver. Echocardiogram showed grade 1 diastolic dysfunction. MRI of hypothalamic pituitary area with olfactory area showed normal anatomy.

Infantile feeding difficulties, developmental delay, hyperphagia, childhood obesity, poor mental development, diabetes mellitus, hypogonadotropic hypogonadism, and short stature lead to work up of genetic cause of obesity with the suspicion of PWS. Cytogenetic study was done and FISH (fluorescence in situ hybridisation) technique was performed to find the genetic abnormality (2). DNA probes were used in the metaphase for regions in chromosome 15 for Prader-Willi SNRPN (15q11)/PML (15q24) genes. They showed micro deletion of the region 15q11-13 found in all the cells studied. Methylation specific PCR revealed the presence of only the methylated band of the promoter region of the SNRPN gene proving the diagnosis of PWS in the patient.

4. Management

He was put on multiple dose subcutaneous insulin regimens to achieve blood glucose control. Medical nutrition therapy and exercise was also started. Hypogonadism was managed with intramuscular depot injections of testosterone once every 3 weeks. Patient was also given Psychiatry consultation for temper tantrums and started on Aripiprazole. Growth hormone therapy was deferred due to possible sleep disordered breathing. Dental consultation was done and he was advised to maintain proper hygiene with chlorhexidine and sodium monofluoro phosphate mouth wash.

5. Discussion

Our patient had features of developmental delay, short stature, feeding difficulties in infancy which subsequently improved, poor mental development, hyperphagia, hypogonadotropic hypogonadism, and type 2 diabetes mellitus. All these fit into the consensus diagnostic criteria for Prader-Willi Syndrome. Prader-Willi Syndrome (PWS) is a complex multisystem genetic disorder that shows great variability, with changing clinical features during a patient's life (4). The syndrome is due to the loss of expression of several genes encoded on the proximal long arm of chromosome 15 (15q11.2-q13). Loss of the paternal chromosomal segment 15q11.2-q12 is principally responsible for PWS. Such a loss can occur by either of two mechanisms: through deletion of the paternal "critical" segment (75%), or through loss of the entire paternal chromosome 15 with the presence of two maternal homologues (uniparental maternal disomy) in approximately 22% of patients. Traditionally, obesity has been a hallmark feature of PWS. Lean body mass is decreased, even in very young infants and toddlers with normal or non-obese BMI (5). This leads to increased fat mass and lower resting energy expenditure, further promoting weight gain and abnormal body composition (6). It has been reported that osteoporosis and increased fractures are seen at increased frequencies in PWS. Fracture rates have been reported as high as 29% in adults with PWS (7). A frequent symptom in PWS patients is excessive sleepiness, which often begins in early childhood and negatively impacts the everyday life of patients (8,9). In a recent study it was shown that the motivation to maintain oral health should be constant for this patient and involve family, since hyperphagia, which is a determinant for obesity, decisively contributes to the evolution of oral diseases (10). Early diagnosis of PWS is important for effective long-term management, and multidisciplinary approach is fundamental to improve quality of life, prevent complications, and prolong life expectancy.

Considering the consensus diagnostic criteria (11), he had 7 major and 4 minor criteria with a total score of 9 (with 8 criteria required for diagnosis for PWS)

6. Conclusion

The unusual aspect of our patient was the fact that in spite of having typical features of PWS, the diagnosis was not made till the age of 23 years. It was only when he developed uncontrolled hyperglycaemia, obesity and presented to us with these problems that appropriate work-up was done to reveal the diagnosis. This reflects the lack of awareness about PWS, as our patient had visited several Paediatricians and Physicians since birth for various health issues but the diagnosis was never made. Our discussion highlights the need to spread awareness about the genetic causes of obesity. Prader-Willi syndrome should be suspected when patients present with similar history and clinical findings.



Figure 1



Figure 2



Figure 3

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