A Rare Association of Obesity, Diabetes Mellitus and Bilateral Cryptorchidism: Prader - Willi Syndrome

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Abstract
Prader-Willi syndrome is a genomic imprinting disorder, characterized by obesity, hyperphagia, mental retardation, short stature and hypogonadism. The presenting signs and symptoms depend upon the age at which the patient is seen. Here we report a case of Prader-Willi syndrome, who presented at 16 years of age with diabetes mellitus and cryptorchidism.

Introduction
The prevalence of adolescent obesity and diabetes mellitus has been increasing dramatically worldwide. The rising prevalence of obesity is due to complex genetic traits that are influenced by environmental factors like increasing availability of energy dense foods and sedentary activity. It has been disappointing that a genetic cause of obesity has been identified in only a very few persons. Obesity is also a component of several rare human genetic syndromes that present with characteristic phenotypes; two important obesity syndromes are Prader-Willi syndrome (PWS; OMIM ≠ 176270) and Bardet-Biedl syndrome (OMIM ≠ 209900). PWS is due to lack of expression of paternally contributed genes on chromosome 15q11–q13 due to deletion or maternal uniparental disomy or imprinting defect1,2. It is also one of the most common microdeletion syndromes. We report a case of PWS complicated by diabetes mellitus, cryptorchidism with delayed puberty and confirmed by methylation sensitive polymerase chain reaction (PCR).

Case Report
A 16-year-old boy presented with excessive weight gain, and short stature. He also gave a history of hyperphagia and absent testis noted since birth. During evaluation for obesity, found to have diabetes mellitus recently. He had no history of osmotic symptoms. He was a second sibling of second degree consanguineous marriage parents. At birth, mother noticed absence of testis on both sides, however she was reassured that it will descend over a period of time. Later, the cryptorchidism had not been evaluated by family members due to the poor socioeconomic status. His motor and language milestones were delayed. He also had learning and speech difficulties with poor scholastic performance and dropped out from school at six years of age.

On examination, his height was 135 cm (< 3rd percentile), and weight was 70 kg (> 97th percentile) with BMI of 38.4 kg/m2. He had dysmorphic facies with narrow bifrontal diameter, almond shaped eyes and thin upper lip (Figure 1). He had bilateral lipomastia. No palpable testicular structure was found in inguino-scrotal region. He also had poorly developed scrotal sac with absent rugosity (Figure 2) and his stretched penile length was only 3 cm, suggestive of micro penis. There was no axillary or pubic hair growth. Systemic examinations were normal except generalized hypotonia.

Neuropsychological evaluation revealed that he had an IQ of 63.

On investigation, hemoglobin was 11 g/dl, total white cell count 8000 × 10³/mm³ and platelet count 333 × 10³/mm³. Blood urea was 15 mg/dL and serum creatinine was 0.8 mg/dL. His fasting and postprandial blood glucose was 205 and 341 mg/dl respectively with HbA1c of 9.5%. Thyroid function tests were normal. His S. prolactin 6.1 µg/L (n, 4.79 – 23.3 µg/L), S. cortisol was 325 nmol/L (n, 171 – 536 nmol/L), LH < 0.1 IU/L (n, 0.27 – 4.2 IU/L), FSH 4.1 IU/L (n, 3.5 – 12.5 IU/L), basal total testosterone was 0.27 ng/ml (n, 3 – 15 ng/ml), and following three days of injection
human chorionic gonadotropin 2000 IU, testosterone increased to 1.72 ng/ml. A USG of abdomen and pelvis showed bilateral, well defined, hypoechogenic lesions measuring 8×5 mm each in the inguinal region raising a possibility of undescended testis and it was confirmed with MRI abdomen.

In view of severe short stature and bone age of 12 years with chronological age of 16 years, growth hormone (GH) stimulation test was performed. His basal GH was 0.13 ng/ml, following 0.25 mg of clonidine, 60 and 90 minutes GH was 3.6 and 6.1 ng/ml respectively. IGF-1 was 130 ng/ml (n, 193 – 731 ng/ml).

In the presence of obesity, short stature, hyperphagia, delayed puberty in the midst of bilateral cryptorchidism, and dysmorphic facies, with biochemical evidence of hypogonadotrophic hypogonadism, a diagnosis of PWS was considered. It was confirmed by DNA based methylation test by PCR method. He was counseled regarding diabetic diet with strict schedule for meals and snacks, and limitation of portion sizes. Pre mixed insulin, metformin therapy was started for glycemic control, course of human chorionic gonadotropins 2000 IU, weekly thrice were initiated. He was referred to urologist for orchidopexy and advised gonadotropins 2000 IU, weekly thrice. He was referred to endocrinologist for growth hormone therapy (2mg/day) was advised for the height gain and improvement in muscle mass and hypotonia.

**Discussion**

The global epidemic of obesity largely explains the dramatic increase in the incidence and prevalence of type 2 diabetes mellitus (T2DM) in adolescents and young adults over the past 20 years. Genome wide association studies (GWAS) have identified many obesity gene variants appear to be involved in pathways affecting energy homeostasis. Although numerous obesity-associated genes have been identified, the known genes are estimated to predict only 5% of obesity risk. The two important obesity associated syndromes are Prader-Willi syndrome (PWS) and Bardet-Biedl syndrome. PWS is an imprinted condition, has a prevalence of 1/30,000 with approximately 70% of the cases due to a de novo deletion in the paternally inherited chromosome 15 q11-q13 region, 25% from a maternal uniparental disomy of chromosome 15, and the remaining 5% due to microdeletions. The obesity in PWS is classically associated with hyperphagia, and is caused by hypothalamic abnormality resulting in lack of satiety. Early counseling, caloric restriction with carbohydrate content as low as 45% and behavioral modification may have more favorable effects on body composition and fat utilization. Prescribed daily physical activity is also important and contributes to improved body composition and resting energy expenditure.

Hypogonadism is a consistent feature of PWS; our patient also had bilateral cryptorchidism, which is seen in 80-90% of males with PWS. Males commonly have cryptorchidism, poorly rugated, underpigmented, hypoplastic scrotum, with small penis as present in our case. HCG therapy may increase scrotal size and penile length, which can improve orchidopexy outcomes and facilitate later standing micropenis. However, there are no published data regarding the efficacy of this practice in patients with PWS. Surgical correction of cryptorchidism should be completed in the first or second year of life. Hypogonadism was classically thought to be hypothalamic in etiology, however the recent evidence has emerged, to support primary gonadal failure as a significant contributor to male hypogonadism.

Type 2 diabetes mellitus has been reported in 25% of adults with PWS with onset at a mean age of 20 years. The mean BMI of those who developed type 2 diabetes in one of the cohort was 37 kg/m². The other manifestations of PWS are short stature, small hands and feet, an abnormal body composition (reduced lean tissue and increased fat mass), developmental delay, mild to moderate intellectual disability, characteristic behaviours and psychological problems. Short stature may be apparent in childhood and is almost always present by the second decade in the absence of growth hormone (GH) replacement. GH therapy decreases fat mass and increases muscle mass. It also has beneficial effect on weight gain, and more importantly, an improvement in cognitive function.

Although consensus clinical diagnostic criteria have been published and validated, diagnosis should not rest on clinical grounds alone. DNA methylation analysis is the only technique that will diagnose all three molecular classes of PWS (deletion, uniparental disomy and imprinting defect) correctly. We performed a methylation sensitive PCR in our case. However, DNA methylation analysis cannot distinguish the molecular class.

**Conclusion**

PWS is complex disorder associated with multiple endocrinopathies, obesity, sleep disorders, and behavioral problems. Individuals with PWS should be treated in a multidisciplinary center familiar with the myriad of issues that must be addressed in the syndrome. Early diagnosis and treatment with GH and HCG have had positive effects for the younger generation with this syndrome.

**References**