

CASE REPORT

Prader-Willi Syndrome: Deletion of Chromosome 15q11.2-q13 in Paternal Allele

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Abstract

Prader Willi Syndrome (PWS) is one of the most common genetic condition of childhood morbid obesity. Absence of expression of the paternally active genes on the long arm of chromosome 15 is responsible for this syndrome. A 4-year-old girl, presented with excessive weight gain since early infancy. She has developmental delay, mental retardation and Her physical features were suggestive of Prader-Willi syndrome. MS PCR detected deletion of the specific chromosomal region 15q11.2-q13 in the paternal allele which is causative of Prader-Willi syndrome. The syndrome has no cure but multidisciplinary approaches are available to improve associated problems. We confirm the case of Prader Willi Syndrome by genetic analysis, which is important for those who present with obesity and mental retardation.

Keywords: Prader-Willi syndrome, genome-wide copy number variation analysis, high resolution chromosome gene imprinting

Introduction

Prader- Willi Syndrome (PWS) is one of the most common genetic condition of childhood obesity. PWS was first described by Andrea Prader and Heinrich Willi in 1956.¹ Prevalence rate of this syndrome is 1 in 10000 to 30000 people worldwide and affects both gender with equal frequency and occurs sporadically.² Absence of expression of the paternally active genes on the long arm of chromosome 15 is responsible for this syndrome. The genetic mechanisms of PWS include:³ a) paternal deletion of 15q11–q13 (70%) b) maternal uniparental disomy (20-25%) c) genomic imprint (2-4%) d) other rare causes like chromosome translocation and microdeletion (<1%).

Clinical diagnostic criteria were established by consensus in 1993. Holm et al established the following diagnostic criteria for Prader-Willi syndrome.⁴ Based on these guidelines, the diagnosis of PWS is likely in children younger than 3 years with 5 points

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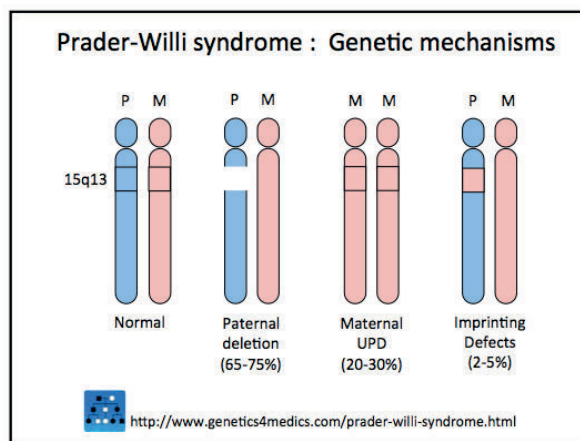


Figure 1: The genetic mechanisms of PWS include: paternal deletion of 15q11–q13, maternal uniparental disomy and genomic imprint

(3 from major criteria) or in older than 3 years with 8 points (4 from major criteria).

- Major criteria (1 point each)
 - CNS - Infantile central hypotonia
 - GI - Infantile feeding problems and/or failure to thrive
 - Nutrition - Rapid weight gain in children aged 1-6 years

- o Craniofacial - Characteristic facial features such as narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, and down-turned mouth
- o Endocrine - Hypogonadism
- o Developmental - Developmental delay and/or mental retardation
- Minor criteria (one half point each)
 - o Neurologic - Decreased fetal movement and/or infantile lethargy
 - o Pulmonary - Sleep disturbance and/or sleep apnea
 - o Endocrine - Short stature for predicted height by mid adolescence
 - o Dermatologic - Hypopigmentation
 - o Orthopedic - Small hands and feet
 - o Orthopedic - Narrow hands with straight ulnar border
 - o Ophthalmologic – Esotropia and/or myopia
 - o Dental - Thick viscous saliva
 - o Otolaryngology - Speech articulation defects
 - o Psychiatric - Skin picking (Some patients with Prader-Willi syndrome have become anemic from chronic rectal bleeding secondary to skin picking.)
 - o Supportive criteria (no points)=urology - High pain threshold and normal neuromuscular evaluation for hypotonia
 - o Gastroenterology - Decreased vomiting
 - o Endocrinology - Ineffective thermoregulation, early adrenarche, and/or osteoporosis, adrenal insufficiency

- o Orthopedics – Scoliosis or kyphosis
- o Developmental - Jigsaw puzzle proficiency

Although prefixed clinical criteria are existed, but the manifestations vary with age and very difficult to diagnose at early age. PWS is characterized by hypotonia and failure to thrive in early life, followed by obesity and hyperphagia.⁵ Hypotonia is prenatal in onset, central in origin, manifested as decreased fetal movement and mild-to-moderate hypotonia persists throughout life.⁶ Patients with PWS develop hypothalamic dysfunction which may lead to several endocrinopathies, including growth hormone deficiency (GHD), hypogonadism, hypothyroidism, central adrenal insufficiency (CAI), and poor bone mineral density. In addition to hypothalamic dysfunction and lack of satiety, individuals with PWS have lower resting energy expenditure. Thus, increased risk for obesity which may be complicated by metabolic syndrome and type 2 diabetes mellitus.⁷ Obesity and its complications are the major causes of morbidity and mortality in individuals with PWS.²

GHD is the most common endocrinopathy, the prevalence is between 40–100%.⁸ Hypogonadism is present in both sexes and manifests as genital hypoplasia, incomplete pubertal development, and infertility. In females, the genital hypoplasia is manifested by small clitoris and labia from birth. Precocious adrenarche occurs in approximately 15–20%.⁹ Central Adrenal insufficiency may present in 60% cases and may causes sudden death in PWS.¹⁰

Table I: Suggested new criteria to prompt DNA testing for Prader-Willi syndrome ¹³

Age at assessment	Features
Birth to 2 years	1. Severe hypotonia and poor suck
2-6 years	1. Hypotonia with poor suck 2. Global developmental delay 3. Short stature and /or decreased growth velocity
6-12 years	4. Hypogonadism/hypogonadism 1. History of hypotonia with poor suck 2. Global developmental delay 3. Excessive eating with central obesity 4. Hypogonadism/hypogonadism
Years through adulthood	1. Cognitive impairment, usually mild intellectual disability 2. Excessive eating (Hyperphagia with obsession, obsession with food) central obesity 3. Hypogonadism and /or typical behavioral problems (temper tantrum and obsessive-compulsive disorders 4. Short stature, small hands and feet

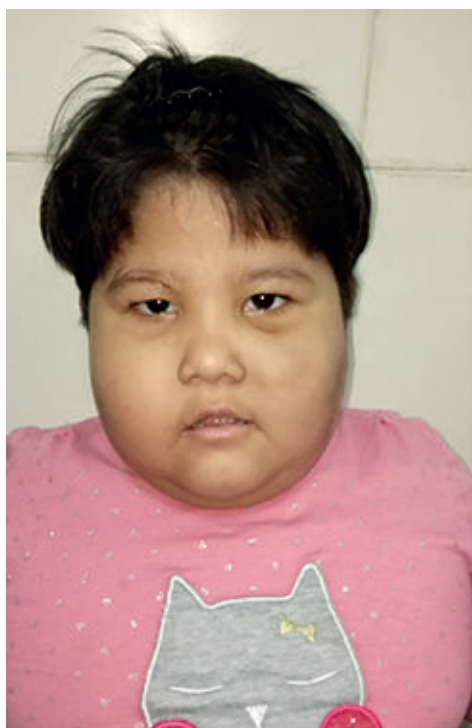
Similar to other endocrinopathies in PWS, the etiology of hypothyroidism is thought to be central in origin. Hypothyroidism has been reported in 20-30% of children with PWS.¹¹ Type 2 Diabetes mellitus is characterized by hyperglycemia and insulin resistance reported in 25 % of PWS.¹²

Management of PWS is age dependent and should include both addressing the consequences of the syndrome. It is recommended that a team approach be used. Early diagnosis and comprehensive care of PWS patients has improved outcomes. However, areas where further research is needed include the etiology and management of PWS.

The Case

J, a four year and 3-month-old girl of non-consanguineous parents, was presented with excessive weight gain since early infancy, hyperphagia and snoring for last 1 year. Her mother was on regular antenatal checkup but experienced less fetal movement and the child was born by caesarean section at term, birth weight was 3200 gm and no history of delayed cry. After birth she had feeding difficulties, less activity and weak cry and got naso-

gastric tube feeding for initial 3 months due to poor sucking and cleft palate. She also had developmental delay. On examination, she had almond shaped eyes, small mouth, thin lip, convex angle of mouth downwards, dental caries, short neck, small hands and feet, mental retardation and delayed speech (Photograph 1a and 1b). Her weight was 34.7 kg (>97th centile), height for age was 99 cm (on 25th centile), projected height below target height, BMI was 34kg/m²(>95th centile), and waist circumference was 62 cm (>90th centile). The patient had 5 major clinical and 5 minor criteria and total points was 7.5(5 from major criteria and 2.5 from minor criteria). Investigation revealed normal thyroid function, cortisol and lipid profile. Her fasting and 2 hours after 1.75gm/kg glucose was 4.7mmol/L and 5.1 mmol/L respectively. Bone age was 4-5 years, X-Ray nasopharynx showed hugely enlarged adenoid, USG of abdomen showed fatty liver grade II, and echocardiography finding was normal. MS PCR detected deletion of the specific chromosomal region 15q11.2q13 in the paternal allele of this child which is causative of Prader-Willi syndrome. We provided multidisciplinary supportive care to the patient and advised for regular follow up.



1a



1b

Photograph 1: Classical facial phenotype of PWS in our patient. She had almond shaped eyes, small mouth, thin lip, convex angle of mouth downwards and short neck (a) small hands and feet and central obesity (b).

Discussion

Prader-Willi syndrome (PWS) is a genetic disorder, resulting from lack of gene expression on the paternally inherited chromosome 15. Both male and female is affected. The most common clinical manifestations of PWS include obesity (84%), hyperphagia (72.7%), mental disability (54.5%), psychomotor delay (50%), and hypotonia (43.18%).¹⁵ Our patient had all these features. El Khattabi mentioned the following features, developmental delay (97%), learning disabilities (97%), obesity (65%), abnormal extremities (65%), behavioral problems (61%), vision anomalies (56%), rounded face/full cheeks (55%), skull features (53%), genital anomalies (11%), sleep disorders (16%) and feeding difficulties (24%).¹⁶ Our patient had few of these features. Infrequently-reported features including skin picking and high pain threshold were not observed in the present patient.¹⁷ Here, we present a patient with the PWS phenotype mutation in the 15q11-q13 region, which would define classic PWS.

Management of PWS requires multidisciplinary care team that includes combination of behavioral therapy, diet managements, speech therapy, exercises and medications.¹⁸ We provide relevant supportive care to the patient. Early diagnosis and intervention allow implementation of reasonable nutrition and physiotherapy programs to prevent obesity and improve motor milestones, decreased resting heart rate, improved aerobic capacity and decreased both body fat and body weight.^{19,20} The most important complications of PWS are related to the cardiovascular and respiratory involvement caused by obesity. These complications are directly responsible for the high incidence of death in children with PWS.²¹ No medications have been found to effectively modify hyperphagia. Encouragement of physical activity, correction of osteopenia, behavioral therapy, identification of endocrine problems and regular follow up may improve the life.

Conclusion

PWS is a complex disorder involving the hypothalamic-pituitary axis, resulting in multiple endocrinopathies, obesity, sleep disorders, and behavioral problems. It is challenging for clinicians to make a diagnosis and management. Genetic analysis is needed to confirm PWS which is important for counselling.

Multidiscipline approach is required to treat ongoing growth, medical, and endocrine disturbances. Parents of children with PWS can be optimistic about the future for their children in light of the improved knowledge for early diagnosis and comprehensive care.

Conflict of Interest: There was no conflict of interest.

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