Case Report

An unusual case of adolescent type 2 diabetes mellitus: Prader–Willi syndrome

Riyas Basheer[1], Muhammed Jasim Abdul Jalal[1], Ramesh Gomez[2]

Departments of [1]Family Medicine and [2]Endocrinology, Lakeshore Hospital and Research Centre, Ernakulam, Kerala, India

Abstract

Prader–Willi syndrome (PWS) is a complex genetic disorder, characterized by neonatal hypotonia, developmental delay, short stature, childhood obesity, hypogonadism, and characteristic facial features. Here we report a 21-year-old male who presented with uncontrolled glycemic status. He was diagnosed to have diabetes mellitus at the age of 15 with osmotic symptoms – polyuria, polydipsia, and polyphagia. In the early period, after diagnosis, his blood sugars were reasonably controlled with oral hypoglycemic agents. However, a year back, he was switched onto insulin therapy due to secondary OHA failure. On examination, his body mass index was 36 kg/m^2. He had bilateral gynecomastia, decreased biparietal diameter, almond shaped eyes with esotropia. He had hypogonadism and also had mild cognitive impairment. He did not have any proximal myopathy or other focal neurological deficits. Hormonal evaluation showed low testosterone and inappropriately normal fluorescence *in situ* hybridization suggestive of central hypogonadism. With fetal and neonatal hypotonia, delayed developmental milestones, hypogonadism, and early onset diabetes, he fulfilled the clinical criteria for the diagnosis of PWS. Multidisciplinary approach of clinicians together with family and social support are essential to bring out the optimal outcome for such syndromic cases.

Keywords: Adolescent type 2 diabetes mellitus, fetal hypotonia, fluorescence *in situ* hybridization, Prader–Willi syndrome

Introduction

Prader–Willi syndrome (PWS) is a complex genetic disorder, characterized by neonatal hypotonia, developmental delay, short stature, childhood obesity, hypogonadism, and characteristic facial features.[1] It is a genomic imprinting disorder caused by a deficiency of paternally expressed gene or genes in chromosome 15 (15q11.3-q13.3 region).[1] This region contains genes that are epigenetically imprinted.

Case Report

A 21-year-old male who presented with uncontrolled glycemic status. He was diagnosed to have diabetes mellitus at the age of 15 with osmotic symptoms – polyuria, polydipsia, and polyphagia. In the early period, after diagnosis, his blood sugars were reasonably controlled with oral hypoglycemic agents (OHAs). However, a year back, he was switched onto insulin therapy due to secondary OHA failure.

He was a second order child of a nonconsanguineous marriage born out of lower segment cesarean section as there was no spontaneous labor postdate and no progression of labor in spite of induction. His birth weight was 2.75 kg. Postdelivery he had a feeble cry and sluggish sucking reflex. His Apgar score was 6 at 1 min and 7 at 5 min. There was no history of neonatal hypoglycemia, hypocalcemia, or seizures and fever with a rash to suggest maternal rubella. There was no history of undescended testes/neonatal jaundice.

There was a gross delay in motor and language development. He started walking only by 3 years. He was able to talk in sentences only by 5 years. He had voracious appetite since the age of 5.

Address for correspondence: Dr. Riyas Basheer, Department of Family Medicine, Lakeshore Hospital and Research Centre, NH-47 Bypass, Nettoor P.O., Maradu, Ernakulam - 682 040, Kerala, India.
E-mail: riyas.salaam@gmail.com

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He passed the higher secondary examination with the help of a scribe.

He had weight gain since the age of 5, and he gained 80 kg by 21 years. He attained puberty by 13 years. He noticed increasing breast tissue since 11 years of age.

On examination, his height was 150 cm (very much below the 5th centile), and weight was 82 kg (above 95th centile) with a body mass index of 36 kg/m^2. He had bilateral gynecomastia [Figure 1a], decreased biparietal diameter, almond shaped eyes [Figure 1b] with esotropia. He had hypogonadism as evidenced by stretched penile length of 4 cm, the testicular volume of 4 ml bilaterally and P3 status. He also had mild cognitive impairment. He did not have any proximal myopathy or other focal neurological deficits. Fundus was normal. All other systems were within the normal limits.

Hormonal evaluation [Table 1] showed low testosterone and inappropriately normal Fluorescence *in situ* hybridization (FSH) suggestive of central hypogonadism. Thyroid function test was normal and he did not have any cortisol insufficiency.

With fetal and neonatal hypotonia, delayed developmental milestones, hypogonadism, and early onset diabetes, he fulfilled the clinical criteria for the diagnosis of PWS.[2]

FISH [Figure 2] was done for the confirmation of our clinical diagnosis which showed microdeletion of the 15q region as evidenced by only single orange band – in contrast to the normal 2 bands (2 aquamarine and green bands – controls). Two hundred areas were examined, and all showed only single orange band signals. While in the controls, all examined areas showed double signals. With FISH, all the eight major diagnostic criteria[2] for PWS [Table 2] were met. These include:

1) Neonatal and infantile central hypotonia 1
2) Feeding problems in infancy
3) Rapid weight gain on after 12 months and before age 6
4) Characteristic facial features
5) Hypogonadism
6) Global developmental delay or learning problems in older children
7) Hyperphagia (excessive appetite)
8) Deletion 15q 11-13.

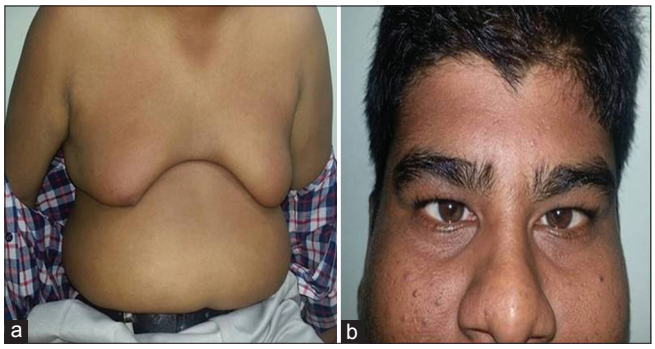


Figure 1 : (a) Gynecomastia and (b) almond shaped eyes with esotropia

We started him on a weight reducing diet plan of 1200 kcal/day. Split mix insulin was started along with metformin to tackle type 2 diabetes mellitus. Depot testosterone was considered in view of hypogonadism. He could not afford growth hormone therapy.

Discussion

PWS was first described by Prader, Labhart, and Willi in 1956.[3] The birth incidence of PWS is 1 in 30,000, and the population prevalence is about 1 in 50,000.[4] Neuroanatomical abnormalities have been found in postmortem hypothalamus of patients with

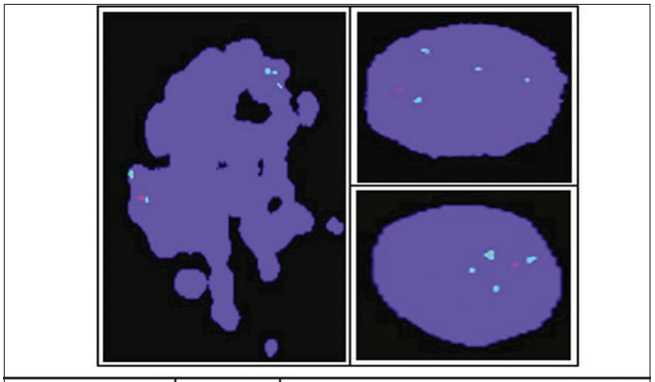
Table 1: Hormonal evaluation

Hormones	Patient's values	Normal values
8 a.m. testosterone (ng/dl)	140	>200
FSH (IU)	8.2	4-18
T4 (μg/dl)	8.2	6.02-12.8
TSH (mIU)	4.7	0.37-5.2
8 a.m. cortisol (μg/dl)	13.7	>12
HbA1c (%)	12.5	<5.7

FSH: Fluorescence *in situ* hybridization; TSH: Thyroid stimulating hormone; HbA1c: Glycated hemoglobin

Table 2: Diagnostic criteria for Prader–Willi syndrome

Criteria	Score
Neonatal and infantile central hypotonia	1
Feeding problems in infancy	1
Rapid weight gain on after 12 months and before age 6	1
Characteristic facial features	1
Hypogonadism	1
Global developmental delay or learning problems in older children	1
Hyperphagia (excessive appetite)	1
Deletion 15q 11-13	1
Total score	8



Probe location on chromosome	Probe Colour	Number of cells with					
		0 signals	1 signal	2 signals	3 signals	4 signals	> 4 signals
15q11-13(SNRPN)	Orange	0	200	0	0	0	0
15p11.2(control)	Aqua	0	0	200	0	0	0
15q22(controls)	Green	0	0	200	0	0	0

Figure 2: Fluorescence *in situ* hybridization

PWS that may underlie the hyperphagia, particularly low oxytocin cell number.

Considering the genetic analysis, paternal chromosomal deletion is most common approximately in 70% of cases.[5] Here, part of chromosome 15 inherited from child's father is missing in the PWS critical gene area. Maternal uniparental disomy is also seen but only in approximately 25% of cases.[5] Here, baby inherits both copies of chromosome 15 from one parent – the mother.

15q11-13 is normally silenced in the maternal chromosome. Only the paternal gene is expressed. At times, the paternal gene can get silenced because of methylation of the 15q11-13 region known as epigenetic mutation.[5]

Management mainly involves motor program with supervised physiotherapy and language training.[6] Supportive tube feeding during infancy can be considered in view of the failure to thrive. Counseling of the parents is the cornerstone of the management of PWS children.[6]

About 25% of PWS patients develop diabetes by the age of 25 years, the mean age of onset being about 20 years.[6] This is primarily attributed to low metabolic rate and hyperphagia.[6,7] Physical activity in PWS is significantly reduced and is related to obesity, hypersomnolence, and persistent poor muscle tone.

Exercise and diet management remains crucial in the management of diabetes in PWS. Initially, insulin sensitizing agents such as metformin may be required with subsequent introduction of the insulin therapy. PWS classically goes through different stages of poor feeding to hyperphagia to satiable feeding behavior.[8]

Angelman syndrome is the maternal counterpart of PWS. It occurs due to deletion of maternal chromosome 15q11-13, paternal uniparental disomy or epigenetic silencing of the maternal E3A gene.[9] These children have more pronounced neurobehavioral abnormalities – seizures, inappropriate laughter, and seizures.

Conclusion

The onset of type 2 diabetes mellitus in early adulthood can be due to rare syndromic causes. Antenatal history of fetal/neonatal hypotonia and childhood history of feeding disorder remains the key to the diagnosis of PWS. Multidisciplinary approach of clinicians together with family and social support are essential to bring out the optimal outcome for such syndromes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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