Case report

Diabetes mellitus in an obese adolescent boy with voracious appetite: An unusual Presentation : Prader-Willi syndrome

Dr.Krishna Shankar G[1], Dr.Soumik Goswami[2] , Dr.Nilanjan Sengupta[3], Dr.Pranab Kumar Sahana[4]

[1]Post doctoral trainee,[2] RMO cum clinical tutor, [3] Professor,[4] Associate Professor.
Department of Endocrinology, Nil Ratan Sircar medical college & hospital, Kolkata, West Bengal, India-700014
Corresponding author: Dr.Krishna Shankar G

Abstract

Prader-Willi syndrome (PWS) is arare cause of obesity and is associated with multipleendocrinopathies including type 2 diabetes mellitus (T2DM). 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 an obese adolescent boy who presented to us with recent onset diabetes. Despite the presence of neurodevelopmental and syndromic associations with obesity, the diagnosis in our patient was delayedby treating physician on account of lack of awareness about PWS.

Keywords: Type 2 Diabetesmellitus (T2DM), obesity, Prader-Willi syndrome (PWS)

Introduction

Prader-Willi syndrome (PWS) is a cause of childhood obesity which occurs rarely with a prevalence of about 1/15,000-1/25,000 live births [1] .PWS was firstdescribed in 1956 by three Swiss doctors - Prader et al [2]. PWS is caused by the lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13and was the first recognized disorder related to genomic imprinting in humans [3]. Here, we discuss a patient, who presented to the endocrinology out-patient department with balonoposthitis, uncontrolled hyperglycemia, and obesity and was found to have PWS on further evaluation.

Description of our patient

Our patient was a 14 year old male, presenting with history of painful micturition and nocturnal enuresis for 1 week.

He was born of non-consanguineous marriage, with his motherbeing 30years and father 45 years old at the time ofbirth. He was delivered by vaginal route at term weighing 2.5 kg. There was a history of birth asphyxiawith delayed cry after birth. He had a shrill cry with poor sucking ability and decreased power in his limbs till 8 months of age. All motor, language and social milestones were delayed. He has an elder sister who is normal. Allhis first degree relatives have no history of similar illness and none of them are obese.

He displayed aggressive violent behaviour towards his family members, threw temper-tantrums, but also showed unusually affectionate behaviour intermittently. His scholastic performance was poor and he had to drop out of school at 8 years. From the age of 3 years, he started eating aggressively and demanded food at frequent intervals with a history of increased weight gain thenceforth but was short compared to his peers.There was associated poor development of external genitalia and secondary sexual characters.

Examination revealed a height of 137cm (< 3rd centile, SDS -2.77, short stature for age) [4, 5], sex

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

adjusted target height of 166.5cm (between 10th to 25th centile), weight of 66kg (> 97thcentile), body mass index (BMI) for age and sex was 34.7kg/m^2 (> 95thpercentile, obese for age and sex) [4, 5]. Waist circumference was 117 cm and hip circumference was 102 cm with Waist Hip Ratio of 1.14. Ratio of upper and lower segment was 0.98 and difference between arm span and height was 1.5 cm.[fig 1]

Pulse rate was 82/min with peripheral pulses equally palpable and blood pressurewas 102/78 mmHg in all four limbs.He had small hands and feet, anarrow face, narrow nasal root, and thin upper lip with downturned corners of the mouth[6][fig 2, 3]. He also hadacanthosis nigricans, low set ears, lipomastia and flat foot with a superficial ulcer. He did not have goitre, purplish striae or polydactyly [Fig 4].Testis wasnot palpable bilaterally with scrotum being Tanner stage 3 andpubic &axillaryhair wereabsent [7]. His stretched penile length was 4 cm [micropenis][8] and he had active balonoposthitis[Fig5]. Cardiovascular, respiratory and abdominal examination was normal.Neurology examination, including dilated fundoscopy was normal. Psychiatric and psychological assessment revealed an IQ of 28±5 with a disability of 90%.

Investigations

The fasting and postprandial plasma glucoseat presentation were 325mg/dl and 504mg/dl respectively while HBA1c was 8.6%.

Lipid profile weretriglycerides – 158mg/dl,LDL-C 118mg/dl,HDL-C-61mg/dl.Liver function test, renal function test and complete hemogram werenormal. Thyroid function, 8 am serum cortisol and plasma ACTH were within normal limits.

Serum IGF1 was low at 47.1ng/ml (220-972 ng/ml),as was total testosterone at <20ng/dl [low for age, sex]. LH was 4.31 mIU/ml andFSH was 8.53 mIU/ml indicating hypogonadotropic hypogonadism.Ultrasonography of abdomen, pelvis & scrotum revealed bilateral underdeveloped testis 2×3 mm and 3×3 mm in the inguinal regions, absent mullerian structures and poorly developed wolffian structures.

Childhood obesity, hypogonadism, poor mental development, diabetes mellitus and short stature lead to work up of genetic cause of obesity with the suspicion of PWS.Cytogenetic study was done. Karyotyping was done with heparinised peripheral blood .The blood culture was set in Karyomax (Gibco, USA) for 72 hours. [Fig 6]Leucocyte culture metaphase karyotype: G'banding showed 46XYkaryotype with no evidence of any structural or numerical abnormality in any of the metaphases studied.Since there was a strong clinical suspicion of Prader Willi Syndrome, FISH (fluorescence in situ hybridisation) technique was performed to find the genetic abnormality [3].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 metaphases 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.[Fig 6]

Management

Patient was treated for balonoposthitis with fluconazole and was put on multiple dose subcutaneous insulin regimen for few days to achieve euglycaemia.Medical nutritional therapy and exercise was also started. After achievement of glycaemic control, insulin was stopped and he was put on glimepiride, metformin and acarbose. Hypogonadism was managed with intramuscular depot injections of testosterone estersadministered triweekly. Patient was also placedunder psychiatry consultation for vocational therapy.The dietary habit of the patient was the most difficult problem

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

to address and prospective efforts are ongoing to modify diet. Recombinant human growth hormone therapy [1]was offered to the boy ,which has been shown to cause weight loss, control polyphagia .The family has postponed the initiation of therapy due to socioeconomic reasons.

Discussion:

Our patient had features of obesity from early childhood, poormuscle tone and suck from birth which subsequently improved,poor mental development, short stature, hyperphagia, cryptorchidism, hypogonadotropichypogonadism, and type 2 diabetes mellitus. All these fit into the consensus diagnostic criteria for PraderWilli Syndrome.Prader-Willi Syndrome (PWS) is a complex multisystem genetic disorder that shows great variability, with changing clinical features during a patient's life. The syndrome is due to the loss of expression of several genes encoded on the proximal long arm of chromosome 15 (15q11.2–q13). 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[9][Table 1], he had 7 major and 4 minor criteria with the total score of9 (with 8 criteria required for diagnosis for PWS).

PWS shows great variability, with different features manifesting during a patients different life stages [10]. As a new born, the individual might suffer from severe hypotonia with feeding problems and global developmental delay. During infancy, these characteristics impede the acquisition of gross motor and language milestones. As a child, there is a development of hyperphagia that can lead to early onset obesity. This is most probably caused by a hypothalamic dysfunction, which is also responsible for growth-hormone deficiency and hypogonadism.Associated T2DM is also aggravated by obesity and hyperphagia.The features which should prompt a genetic testing for Prader- Willi Syndrome according to age at assessment [10].

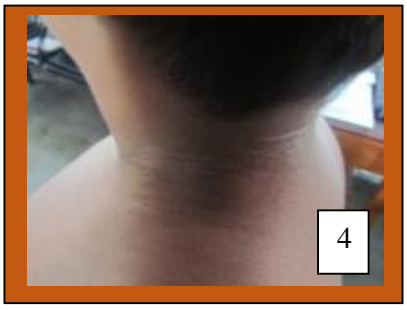
The unusual aspect of our patient was the fact that in spite of having typical features of PWS, the diagnosis was not made till the age of 14 years. It was only when he developed uncontrolled hyperglycaemia,balonoposthitis and presented to us with these problems that appropriate work-up was done to reveal the diagnosis. This reflects the lack of awareness about PWS, as our patient had visited several primary care physicians since birth for a variety of health issues but the diagnosis was never made. PWS presenting initially as diabetes in an obese adolescent is rarely reported in the literature which makes the presentation of our patient an unique one. Our discussion highlights the need to spread awareness about the genetic causes of obesity.

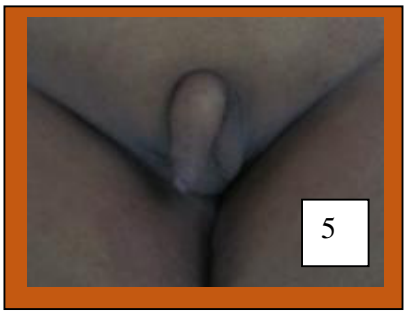
Conclusion

We have described a case of PWS whichwas diagnosed in adolescenceafter presenting to us with diabetes.This case is important since the syndromic cause of obesity was never diagnosed from childhood even when typical features of PWS was present.

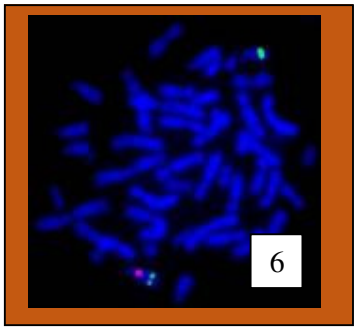
TABLE 1

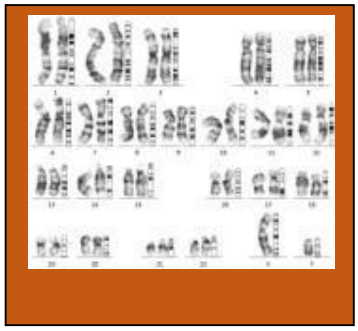
MAJOR CRITERIA	Minor criteria
Hypotonia in neonatal period	Decreased inutero activity
Failure to thrive	Behavioural abnormalities
Rapid weight gain after 1st year	Sleep disturbances/sleep apnea
Characteristic facies	Short stature
Hypogonadism[small phallus,cryptorchidism,delayed puberty]	Hypopigmentation
Developmental delay	Small hands and feet
Hyperphagia	Narrow hand with straight ulnar border
Deletion 15q11	Refractive error
	Articulation difficulty
	Viscous saliva
	Skin picking





www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858





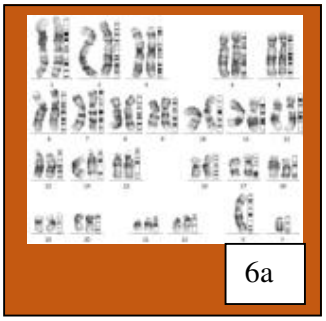


Figure number	Caption for figure
Figure 1	profile picture- 14 yr old male with obesity
Figure 2	PWS with low set ears,thin upper lip,downturned corners of mouth
Figure 3	PWS with low set ears,thin upper lip,downturned corners of mouth
Figure 4	Acanthosis nigricans
Figure 5	cryptorchidism, micropenis, and balonoposthitis
Figure 6	Karyotyping KARYOTYPING: done in heparinised peripheral blood ,showed normal 46,XY ,karyotype in 20 metaphases analysed.
Figure 6a	FISH[fluorescence in situ hybridisation] REPORT. Metaphase showing 2 Green and 1 Orange signals. Microdeletion of the region 15q11-13 is seen in all the metaphases studied

References

1. Elena G, Bruna C, Benedetta M, Stefania DC, Giuseppe C. Prader-Willi syndrome: Clinical aspects. J Obes 2012. 2012 473941. [PMC free article] [PubMed]
2. A. Prader, A. Labhart, and H. Willi, “Einsyndrom von adipositas .....” vol. 86, p. 1260, 1956.
3. D. J. Driscoll, M. F. Waters, C. A. Williams et al., “A DNA methylation imprint, determined by the sex of the parent, distinguishes the Angelman and Prader-Willi syndromes,” Genomics, vol. 13, no. 4, pp. 917–924, 1992.
4. http://www.cdc.gov/growthcharts/data/set1clinical/cj41c023.pdf
5. Pediatrics in Review Vol.34 No.4 April 2013 187,188,189
6. de Souza MA, McAllister C, Suttie M, Perrotta C, Mattina T, Faravelli F, Forzano F, Holland A, Hammond P.Am J Med Genet A. 2013 Oct;161A(10):2453-63. doi: 10.1002/ajmg.a.36100. Epub 2013 Aug 5.PMID: 23918156 [PubMed - indexed for MEDLINE]
7. Arch Dis Child. 1970 Feb; 45(239): 13–23.,PMCID: PMC2020414,Variations in the Pattern of Pubertal Changes in Boy,W. A. Marshall and J. M. Tanner
8. Age-related changes in stretched penile length in comparison with data from a previous study conducted in 1987,Modified from Chung KH, et al. Korean J Urol 1987;28:255-8, with permission of The Korean Urological Association
9. V. A. Holm, S. B. Cassidy, M. G. Butler et al., “Prader-Willi syndrome: consensus diagnostic criteria,” Pediatrics, vol. 91, no. 2, pp. 398–402, 1993.
10. M. Gunay-Aygun, S. Schwartz, S. Heeger, M. A. O'Riordan, and S. B. Cassidy, “The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria,” Pediatrics, vol. 108, no. 5, article E92, 2001.