Morbid obesity in an adolescent with Prader-Willi syndrome

Vitorino Modesto dos Santos, MD, PhD[1,2], Fernando Henrique de Paula, MD[2], Ernesto Misael Cintra Osterne, MD[2], Natalia Solon Nery, MD[2], Thiago Zavascki Turra, MD[2].

Prader-Willi syndrome is an uncommon multisystem genetic disorder caused by defects of chromosome 15 (15q11-q13), often due to deletions or uniparental disomy. The syndrome is characterized by neonatal hypotonia, dysmorphic facial features, short stature, motor and mental disabilities, behavioral changes, hyperphagia, precocious obesity and hypogonadotropic hypogonadism. We present a 17 year-old woman, with a previous genetic diagnosis of Prader-Willi syndrome and BMI of 74 Kg/m^2, that was admitted in anasarca, with marked cyanosis, dyspnea and oliguria. She presented high levels of blood urea, creatinine and aminotransferases, in addition to hyperkalemia and hyperuricemia. She had been in regular use of fluoxetine during the last six months, and evolved with severe high blood pressure and respiratory failure, which needed intensive care support. Moreover, sequels and clear signs of recent self-injuries were observed in her trunk, forearms and hands. The findings of morbid obesity, anasarca, self-injury, hyperuricemia and hypoxemia in Prader-Willi syndrome are emphasized (Rev Méd Chile 2009: 137: 264-8).
*(**Key words:** Edema; Fluoxetine; Obesity, morbid; Prader-Willi syndrome)*

Obesidad mórbida en una adolescente con síndrome de Prader-Willi

El síndrome de Prader-Willi es un desorden multisistémico infrecuente causado por defectos genéticos del cromosoma 15 (15q11-q13), debido a deleciones o disomía uniparental. Se caracteriza por hipotonía neonatal, dismorfias faciales, baja estatura, incapacidades motoras y mentales, problemas conductuales, hiperfagia, obesidad precoz e hipogonadismo hipogonadotrófico. Presentamos una mujer de 17 años, con IMC de 74 Kg/m^2 con diagnóstico genético previo del síndrome que ingresó con anasarca, intensa cianosis, disnea y oliguria. Presentaba elevación plasmática de urea, creatinina y aminotransferasas, asociadas con hiperkalemia e hiperuricemia. Había utilizado regularmente fluoxetina durante los seis meses precedentes y evolucionó con hipertensión arterial severa e insuficiencia respiratoria, que requirieron de cuidados intensivos. Además, se constataron cicatrices y claras señales de automutilación reciente en su tronco, antebrazos y manos. Se destacan los hallazgos de obesidad mórbida, anasarca, automutilación, hiperuricemia e hipoxemia en el síndrome de Prader-Willi.

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[1]Catholic University Medical Course, and Department of Internal Medicine from the Armed Forces Hospital (HFA), Brasilia-DF, Brazil. [2]Department of Internal Medicine from the HFA.

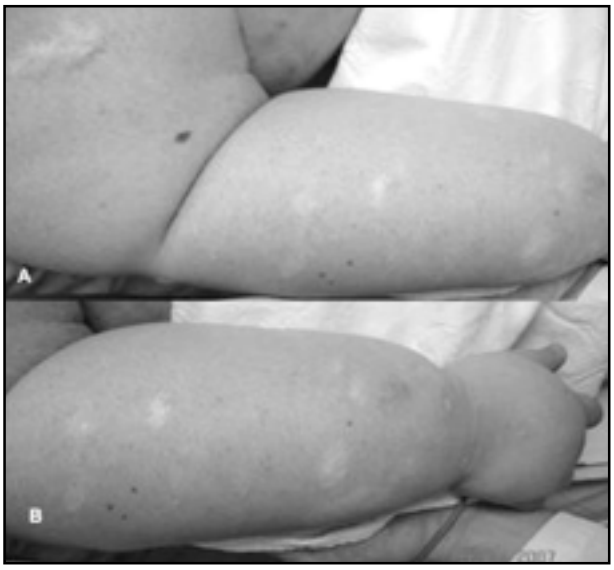
Address to: Prof. Dr. Vitorino Modesto dos Santos. SMPW Quadra 14 Conjunto 2 Lote 7 Casa A, 71.745-140, Brasília-DF, Brazil. Tel.: 61 33802666. Fax: 61 32331599. E mail: vitorinomodesto@gmail.com

The Prader-Willi syndrome (PWS) was first described by A Prader, A Labhart and H Willi in 1956[1], and is a neurodevelopmental condition associated with early onset of childhood obesity[2]. The prevalence of PWS is 1:15,000-25,000[3], and the associated genetic changes involve deletions of the paternally derived chromosome 15, maternal disomy of chromosome 15, imprinting center mutations, and translocations[4-8]. The PWS clinical spectrum includes: decreased fetal movement; neonatal hypotonia; infantile feeding problems and failure to thrive; childhood-onset hyperphagia; morbid obesity; facial dysmorphic features; mental retardation; reduced growth-hormone (GH) secretion; hypogonadism; short stature for family; small and narrow hands and feet for height and age; low lean body mass; behavioral abnormalities; sleep disturbances; and self-injury tendency[2,3,5-7]. PWS has been considered an uncommon condition, and may be underdiagnosed because the features that raise diagnostic suspicion evolve over time or may be nonspecific; therefore, the clinical criteria must be assessed in accordance to the patient's age range[7]. The suspected cases can be confirmed by molecular resources including methylation, cytogenetic, or fluorescence *in situ* hybridization tests[6-8].

Hormone treatment for GH deficiency and hypogonadism will benefit patients with PWS[5,9], resulting in cognitive, emotional and social positive effects[10]. However, more severe obsessive-compulsive and self-injury problems call for a special psychiatric attention and treatment[11]. Selective serotonin reuptake inhibitors (SSRIs) as fluoxetine have been effective to treat compulsivity and maladaptative behaviors[12]. Because of increased morbidity and premature mortality, often associated with hyperlipidemia and coronary disease, preventive measures in addition to clinical and surgical control of morbid obesity have been a major objective in the treatment of cases with PWS[9,13,14].

Case report

A 17-year-old woman with diagnosis of Prader-Willi syndrome during early infancy was admitted with BMI of 74 Kg/m^2, 147 cm in height, in anasarca and with marked cyanosis, dyspnea and oliguria. She presented left flank and lumbar colic pain. She was in use of fluoxetine for six months, and evolved with severe high blood pressure and respiratory failure, that needed intensive care support. Huge edema and conspicuous self-injury signs were seen on her trunk, forearms, hands and fingers (Figures 1 and 2). Menarche occurred by 14 years, when she weighed 89.5 Kg and was 139 cm in height. Admission tests showed: red cells 6,72 x 10^9/mm^3, hemoglobin 17.6g/dL, hematocrit 55.7%, MCV 83 fL, white cells 8.1 x 10^6/mm^3 and platelets 229 x 10^6/mm^3; sodium 136 mEq/L, potassium 6.3 mEq/L, magnesium 2.8 mEq/L



Figures 1A and 1B. Evident signs of morbid obesity and anasarca, in addition to sequels of self-injury observed on admission.

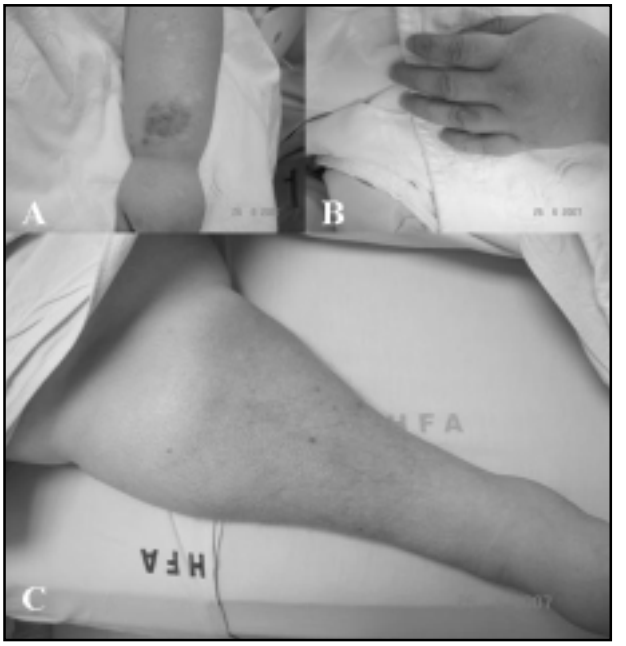


Figure 2A. Small and narrow hand for age, reduction of obesity and absence of edema. Figure 2B. Self-injury change in the fourth left finger. Figure 2C. Feature of the right inferior limb erysipela, near to hospital discharge.

and phosphorus 3.4 mg/dL; urea 66.2 mg/dL, creatinine 1.2 mg/dL, glucose 105 mg/dL and uric acid 13.2 mg/dL; normal serum ALT, AST and amylase levels. Urinalysis detected urate crystals, and urine culture was negative. Further data were: cortisol level 9.20 μg/dL (normal range 6.2 to 19 μg/dL); normal TSH (2.9 μUI/mL) and free-T4 (0.97 ng/dL); serum complement 188 U/CAE (normal ≥ 60 U/CAE) and normal C3 and C4; anti-DNA antibody 34.1 UI/mL (normal ≤ 35 UI/mL); normal ASLO 72.1 UI/mL; rheumatoid factor 9.56 U/mL (normal ≤ 15 U/mL); and negative tests for HIV and C and B hepatitis viruses.

In addition to fluoxetine, her initial treatment included diuretic, antihypertensive and allopurinol, and oxygen by catheter or mask. During the first two weeks of admission, she had respiratory function deterioration, with sleep apnea episodes, that improved with intensive care support (Table 1) and loss of 30 Kg in her body weight. Another occurrence was erysipelas in her legs (Figure 2C), successfully treated with penicillin. After 50 days of admission, she was discharged to home care assistance.

Discussion

This Brazilian adolescent presented typical PWS dysmorphic features, hyperphagia, morbid obesity, mental retardation, self-injury, sleep apnea, nephrolithiasis, and anasarca. The initial concern was about the origin of edema associated with morbid obesity, which included a differential diagnoses with Cushing syndrome, hypothyroidism, nephrotic and nephritic syndromes. The normal cortisol, as well as normal TSH and free-T4 levels discarded the hypotheses of Cushing syndrome and hypothyroidism. Furthermore, the normal serum complement and C3 and C4 fractions, normal anti-DNA antibody, ASLO and rheumatoid factor, in addition to negative tests for HIV and C and B hepatitis viruses, and unremarkable urinalysis practically ruled out glomerulonephritis and nephrotic syndrome. Other causes of edema could be heart or hepatic failure; nevertheless, there were no physical or complementary data to support these possibilities. Additional hypotheses included adverse effects of fluoxetine, as the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)[15] and/or paradoxal weight gain[16]. Although a rapid loss of weight was observed following the fluoxetine interruption, the patient did not show hyponatremia or hypokalemia. The low caloric diet also played an important role in her clinical improvement, with gradual lessening of symptoms related to pulmonary hypoventilation (snoring, exercise dyspnea, cyanosis and sleep apnea)[17,18]. The benefical effects of weight loss and

Table 1. Comparative hematological data between the use of Catheter/Venturi mask and the nocturnal BiPAP

Hematological data	Catheter / Venturi mask June 12, 2007	Nocturnal BiPAP August 7, 2007
Red cells ($x10^{12}/mm^3$)	6,12	5,23
Hemoglobin (g/dl)	15,6	13,9
Hematocrit (%)	50,6	43,4
MCV (fl)	83	83
White cells ($x10^9/mm^3$)	8.2	10,7
Segmented (%)	69	76
Neutrophils (%)	69	76
Eosinophils (%)	1	3
Lymphocytes (%)	18	15
Monocytes (%)	12	6
Platelets ($x10^9/mm^3$)	239	369

BiPAP: Bilevel Positive Airway Pressure.

Table 2. Comparative gasometrical data including the first day of admission and the weight-loss phase (near one month before the hospital discharge)

Hospital admission June 6, 2007	Fluoxetine withdrawal June 18, 2007	Weight-loss phase July 2, 2007
Ambient air	Catheter/Venturi mask	Nocturnal BiPAP
pO2: 82.4 mmHg	pO2: 66 mmHg	pO2: 106 mmHg
pCO2: 67.2 mmHg	pCO2: 87 mmHg	pCO2: 61.7 mmHg
SaO2: 92.7 %	SaO2: 92%	SaO2: 97.9%
pH: 7.21	pH: 7.41	pH: 7.41
HCO3: 20.8 mEq/l	HCO3: 54.0 mEq/l	HCO3: 34.9 mEq/l
BE:-0.7	BE: 23	BE: 13.1

of the non invasive mechanical ventilation on the respiratory parameters are shown in Table 2. Worth of note is also the finding of erysipelas in the legs of a patient with morbid obesity, which is very often associated with drainage impairment both through the venous and the lymph vessels from the legs.

The patient also presented a colicky pain due to a kidney stone of uric acid. Although nephrolithiasis has been rarely reported in PWS, the hyperuricemia and urine uric acid crystals could be associated with overeating and purine overproduction[19]. Interestingly, the Lesch-Nyhan syndrome shares with PWS the following features: cognitive deficit, attention and psychomotor delay and self-injury behavior, in addition to hyperuricemia, urate cristaluria and nephrolithiasis. Notwithstanding, Lesch-Nyhan syndrome is a very rare inborn disturbance of the purine metabolism almost exclusive of males[20].

The study of the present case underlined some questions to be considered about PWS. First, although clinical scores are helpful for diagnosis and follow-up of PWS suspected cases, the features must be considered in accordance to age range as follows: 1) Birth to 2 years - hypotonia with poor suck; 2) Two to 6 years - hypotonia with history of poor suck, and global developmental delay; 3) Six to 12 years - history of hypotonia with poor suck, develo-

pmental delay, excessive eating, and central obesity (if uncontrolled); and 4) 13 years through adulthood - cognitive impairment, excessive eating, central obesity (if uncontrolled), hypothalamic hypogonadism, and typical behavior problems[7].

Second, although SSRIs have been useful for management of the obsessive-compulsive and self-injurious behaviors in people with PWS, risk-benefits should be considered. Third, the occurrence of SIADH due to SSRIs must be enrolled among the etiologic factors of anasarca in patients with PWS, in special with a concomitant use of diuretics. Fourth, the respiratory disturbances related to morbid obesity are often severe and life threatening, but may be favorably influenced by a sustained program of weight loss. Bariatric surgery has been effective to treat morbidly obese patients with sleep apnea, and may result in appetite control with durable weight loss, lower mortality and better quality of life; however, the results in PWS may be poorer than in normal obesity[14].

Lastly, the earliest as possible obesity prevention plays a major role in the quality of life of individuals with PWS. Furthermore, in spite of all the available clinical and surgical tools, the successful weight loss and maintenance is hardly accomplished.

References

1. Prader A, Labhart A, Willi H. Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myotonieartigen Zustand im Neugeborenenalter. *Schweiz Med Wochennschr* 1956; 86: 1260-1.
2. Miller JL, Goldstone AP, Couch JA, Shuster J, He G, Driscoll DJ et al. Pituitary abnormalities in Prader-Willi syndrome and early onset morbid obesity. *Am J Med Genet A* 2008; 146A: 570-7.
3. Eiholzer U, L'Allemand D, Rousson V, Schlumpf M, Gasser T, Girard J et al. Hypothalamic and gonadal components of hypogonadism in boys with Prader-Labhart-Willi syndrome. *J Clin Endocrinol Metab* 2006; 91: 892-8.
4. Bittel DC, Kibiryeva N, Butler MG. Expression of 4 genes between chromosome 15 breaking points 1 and 2 and behavioral outcomes in Prader-Willi syndrome. *Pediatrics* 2006; 118: e1276-e1283.
5. Burman P, Ritzen EM, Lindgren AC. Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev* 2001; 22: 787-99.
6. Cortés F, Alliende MA, Barrios A, Curotto B, Santa María L, Barraza X et al. Caracterización clínico-genético-molecular de 45 pacientes chilenos con síndrome de Prader Willi. *Rev Méd Chile* 2005; 133: 33-41.
7. Gunay-Aygun M, Schwartz S, Heeger S, O'riordan MA, Cassidy SB. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. *Pediatrics* 2001; 108: E92.
8. Santa María L, Curotto B, Cortés F, Rojas C, Alliende MA. Diagnóstico molecular de los síndromes de Prader-Willi y de Angelman: análisis de metilación, citogenética y FISH. *Rev Méd Chile* 2001; 129: 367-74.
9. Youlton R. Síndrome de Prader-Willi. Tratamiento com hormona de crecimiento en dos casos. *Rev Méd Chile* 2001; 129: 1186-90.
10. Höybye C, Thorén M, Böhm B. Cognitive, emotional, physical and social effects of growth hormone treatment in adults with Prader-Willi syndrome. *J Intellect Disabil Res* 2005; 49: 245-52.
11. Kim JW, Yoo HJ, Cho SC, Hong KE, Kim BN. Behavioral characteristics of Prader-Willi syndrome in Korea: comparison with children with mental retardation and normal controls. *J Child Neurol* 2005; 20: 134-8.
12. Dykens E, Shah B. Psychiatric disorders in Prader-Willi syndrome: epidemiology and management. *CNS drugs* 2003; 17: 167-78.
13. Braghetto I, Rodríguez A, Debandi A, Brunet L, Papapietro K, Pineda P et al. Síndrome Prader-Willi asociado a obesidad mórbida: tratamiento quirúrgico. *Rev Méd Chile* 2003; 131: 427-31.
14. Scheimann AO, Butler MG, Gourash L, Cuffari C, Klish W. Critical analysis of bariatric procedures in Prader-Willi syndrome. *J Pediatr Gastroenterol Nutr* 2008; 46: 80-3.
15. Twardowschy CA, Bertolucci CB, Gracia CM. Pontine and extrapontine osmotic myelinolysis after the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) associated with fluoxetine. *Arq Neuropsiquiatr* 2007; 65: 858-64.
16. Kohn Y, Weizman A, Apter A. Aggravation of food–related behavior in an adolescent with Prader–Willi syndrome treated with fluvoxamine and fluoxetine. *Int J Eat Disord* 2001; 30: 113-7.
17. Deschildre A, Martinot A, Fourier C, Nguyen-Quang JM, Hue V, Derambure P et al. [Effets of hypocaloric diet on respiratory manifestations in Prader-Willi syndrome]. *Arch Pediatr* 1995; 2: 1075-9.
18. Jacob SS, Jacob JJ, Paul TV. Foreign body aspiration in a boy with Prader-Willi syndrome. *Singapore Med J* 2008; 49: e12.
19. Asanuma H, Nagatsuma K, Baba S, Murai M. [A case of Prader-Willi syndrome accompanied with a renal stone]. *Hinyokika Kyio* 1998; 44: 37-9.
20. Torres RJ, Puig JG. Hypoxanthine-guanine phosphoribosyltransferase(HPRT) deficiency: Lesch-Nyhan syndrome. *Orphanet J Rare Dis* 2007; 2: 48 [Epub ahead of print].