Morbid obesity in an adolescent with Prader-Willi syndrome

Vitorino Modesto dos Santos, MD, PhD1,2, Fernando Henrique de Paula, MD2, Ernesto Misael Cintra Osterne, MD2, Natalia Solon Nery, MD2, Thiago Zavascki Turra, MD2.

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/m², 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, sequelas 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).

(Ky 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 delecciones 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/m² 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 anteriores y evolucionó con hipertensión arterial severa e insuficiencia respiratoria, que requirieron de cuidados intensivos. Además, se constataron cicatrices y claras señales de autómutilación reciente en su tronco, antebrazos y manos. Se destacan los hallazgos de obesidad mórbida, anasarca, autómutilación, hiperuricemia e hipoxemia en el síndrome de Prader-Willi.


1Catholic University Medical Course, and Department of Internal Medicine from the Armed Forces Hospital (HFA), Brasilia-DF, Brazil. 2Department 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, Brasilia-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, and is a neurodevelopmental condition associated with early onset of childhood obesity. The prevalence of PWS is 1:15,000-25,000, and the associated genetic changes involve deletions of the paternally derived chromosome 15, maternal disomy of chromosome 15, imprinting center mutations, and translocations. 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. 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. The suspected cases can be confirmed by molecular resources including methylation, cytogenetic, or fluorescence in situ hybridization tests.

Hormone treatment for GH deficiency and hypogonadism will benefit patients with PWS, resulting in cognitive, emotional and social positive effects. However, more severe obsessive-compulsive and self-injury problems call for a special psychiatric attention and treatment. Selective serotonin reuptake inhibitors (SSRIs) as fluoxetine have been effective to treat compulsivity and maladaptive behaviors. 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.

**Case report**

A 17-year-old woman with diagnosis of Prader-Willi syndrome during early infancy was admitted with BMI of 74 Kg/m², 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 10⁹/mm³, hemoglobin 17.6g/dL, hematocrit 55.7%, MCV 83 fL, white cells 8.1 x 10⁶/mm³ and platelets 229 x 10⁶/mm³; 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.
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 µU/mL) and free-T4 (0.97 ng/dL); normal 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 beneficial effects of weight loss and...
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\textsuperscript{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\textsuperscript{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, develop-
mental 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 problems7.

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 obesity14.

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