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CASE REPORT

Severe respiratory insufficiency in Prader- Willi syndrome: A case report

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Abstract

The authors describe the case of a female child, 6 years, diagnosed in the neonatal period with Prader-Willi syndrome (PWS) that evolved to severe respiratory failure due to community-acquired pneumonia. Patient obese, required prolonged invasive ventilation and intensive care. PWS is a genetic disorder resulting from the absence of expression of paternal genes on chromosome number 15 whose behavioral symptoms to hyperphagia and binge eating, being the most common genetic cause of obesity. This study aims to draw attention to PWS and its complications with increased risk in mortality of children with this syndrome: respiratory failure resulting muscle hypotonia and obesity characteristic of these patients. Finally, the article provides a discussion of its clinical manifestations and the approach of this important risk factor.

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INTRODUCTION

In 1956, Prader, Labhar, and Willi described a condition with a phenotype consisting of short stature, obesity, hypogonadism, mental retardation, and hypotonia in infancy which they referred to as Prader-Willi Syndrome (PWS). The prevalence of PWS is approximately 1 in every 10,000 to 30,000 live births, and it affects both sexes equally. It is a complex multisystem disease with endocrine-hypothalamic dysfunction.

It is characterized by two distinct phases: first, the newborn exhibits hypotonia, feeding difficulty with little or no suckling, hypogonadism, peculiar features such as almond-shaped eyes, decreased bifrontal diameter, a triangular-shaped mouth, and delayed psychomotor development. Hypotonia is not progressive and tends to improve between 8 and 11 months of age. Next, the second phase begins, in which hyperphagia and obesity predominate[1].

In studies of the treatment of PWS, interest has been growing around the management of conditions associated with a poor prognosis, particularly obesity[2]. Respiratory failure appears to be a frequent cause of death, most commonly through obstructive apnea[3].

CASE REPORT

A female patient referred to as K.K.G.B. was 6 years of age, weighing 62 kg, born in Boston (USA), now a resident of Galilee, Minas Gerais in Brazil, was admitted to the Pediatric Urgent Care of Governador Valadares City Hospital (HMGV) on February 14, 2016 with respiratory failure. Upon admission, she was found to have central cyanosis and dyspnea. The mother reported an unmeasured low-grade fever and productive cough for the 2 days prior to admission. No other complaints.

Physical examination revealed agitation, which was alternating with periods of drowsiness, verbalization, and sweating; the patient was afebrile. Cardiovascular system: regular cardiac rhythm in two stages, with normal sounds and without murmurs. Heart rate: 134 bpm. Blood pressure: 130/50 mmHg; Respiratory system: rhonchi and slight wheezing. Respiratory rate: 53 breaths per minute. Oxygen saturation of 87% in room air. Abdomen: distended and normotensive without visceromegaly. Genitourinary system: external female genitalia with no abnormalities.

Oxygen therapy was initiated through a face mask with reservoir, and oxygen saturation improved to 93%. Posterior and anterior chest X-rays were ordered, which showed bilateral diffuse alveolar infiltration, and laboratory tests with the following results: Hemoglobin 14.0 g/dL Hematocrit 43%, leukocytes 29,300/mm^3, band cells 23%, segmented cells 68%, lymphocytes 10%, platelets 260,000/mm^3, C-reactive protein (CRP) 140.7mg/dL, potassium 5.7 mmol/L, sodium 143 mmol/L, triglycerides 95mg/dL, calcium 10.1 mg/dL, total cholesterol 226 mg/dL, Gamma glutamyl transferase 120U/L, urea 18 mg/dL, and creatinine 0.6 mg/dL.

The patient was admitted with a diagnosis of community-acquired pneumonia and amoxicillin with clavulanate was initiated intravenously.

History of Previous Pathologies

Child with Prader-Willi syndrome diagnosed in the neonatal period. Hospitalized in the intensive care unit for two months. She received at-home oxygen therapy until 2 years of age for apnea and was monitored by neurologists and endocrinologists for 6 years. Diagnosed with epilepsy. Taking 50 mcg/day of levothyroxine and 100 mg/day of phenobarbital.

On the second day of hospitalization, invasive mechanical ventilation was initiated due to the worsening of the patient's respiratory and radiological condition. She was diagnosed with acute respiratory distress syndrome (ARDS) (Figure 1). Exams showed significant leukocytosis with an increase in band cells and elevated CRP. Levofloxacin and clindamycin were initiated. The patient remained hemodynamically stable, sedated, and continuously medicated. She was transferred to the pediatric intensive care unit, where she remained for 23 days. She required high ventilation parameters (inspiratory pressure: 34; PEEP: 10; FIO_2: 0.7, Volume: 200 ml).



Figure 1. Child with PWS, morbidly obese, on mechanical ventilation due to severe respiratory failure.

Upon admission to the ICU, she exhibited worse radiological results, worse laboratory test results, and fever. Treatment for sepsis secondary to pneumonia associated

with mechanical ventilation (MV) with meropenem and polymyxin was continued for 10 days. The patient exhibited gradual improvement. She was extubated and remained on non-invasive ventilation (NIV) for only a few hours. Since then, she has had a nasal catheter (1-2 L/m).

Complications during hospitalization included thrush in diaper region and cervical region, for which topical nystatin was administered. The lesions worsened and spread to the back. The patient was started on 150 mg of fluconazole. She was monitored by the endocrinology team for appetite control and was given topiramate at 50 mg/day.

She was then transferred to the pediatric ward. She was clinically stable after the 26th day of hospitalization. She was discharged with outpatient follow-up and continuous use of medications.

Main results of laboratory tests during hospitalization (Table 1).

Table 1. Main results of laboratory tests during hospitalization.

Laboratory Tests	Day of Hospitalization						
	1st	4th	5th	8th	11th	14th	25th
Total Leukocytes (x 10^3/mm³)	29.3	15.7	-	-	-	24.0	13.0
Band Cells (%)	23	19	-	-	-	10	7
Segmented Cells (%)	68	54	-	-	-	60	50
Lymphocytes (%)	10	17	-	-	-	25	35
Hemoglobin (g/dL)	14.0	11.6	-	-	-	10.0	12.4
Hematocrit (%)	43	35.7	-	-	-	32	-
Platelets (x 10^3/mm³)	260	245	-	-	-	-	41.5
C-Reactive Protein	140.7	88.5	-	46.4	-	160	17.7
Arterial Blood Gas							
pH			7.33	7.42	7.44		
pO_2 (mmHg)			72	68	81		
pCO_2 (mmHg)	-	-	47.4	38	30.8	-	-
Bicarbonato (mEq/L)			23	24.8	22.4		
Base Excess			0.8	0.4	3		

DISCUSSION

Recent data indicate that the main cause of mortality in PWS is respiratory failure or cardiac insufficiency. In many cases, death seems to be triggered by acute pulmonary infections (pneumonia), and a contributing factor seems to be a decrease in respiratory effort and reflexes compensating for the hypotonia that characterizes the syndrome[4]. Individuals with PWS have a mortality rate of 3% per year. When compared to subjects with delayed neuropsychomotor development or obesity due to other causes, the relative risk of death is six times higher[5].

Its etiology involves three different mechanisms: deletion, uniparental disomy (20% to 25%) and a defect in the imprinting center (1% to 2%). Approximately 75% of cases exhibit microdeletion in the 15q11.2-q13 region of paternal origin, which can be detected only by high-resolution cytogenetic studies or by fluorescence in situ hybridization (FISH)[6,7].

The diagnosis is made in 99% of cases on the SNRPN/SNURE gene methylation test, which is able to demonstrate deletion, uniparental disomy, and defects in the imprinting center in the critical region of chromosome 15. However, in order to understand the exact mechanism of this syndrome, a study of polymorphic markers that can identify the three mechanisms mentioned must be performed[6,7].

The criteria for clinical diagnoses were established by Holm et. al.[8] (1993). For children under 3 years of age, a total of 5 points is required (3 of which must be major criteria) and for children over 3 years, a total of 8 points is required (4 of which must be major criteria). Major criteria (1 point each): Central hypotonia, difficulties eating or feeding, early obesity, characteristic facial features, hypogonadism, mental retardation. Minor criteria (0.5 points each): decreased fetal movements, typical behavior disorders, sleep apnea, short stature, hypopigmentation, small hands and feet, exotropia, myopia, excess saliva, speech impediments, and the habit of pinching the skin. Support criteria (no points): high pain threshold and vomiting, temperature instability, scoliosis and /or kyphosis, early adrenarche, osteoporosis, abnormal ability to solve puzzles, normal neuromuscular exam results[6].

Severe hypotonia is observed consistently at birth and during the neonatal period and PWS must therefore be considered in all inexplicable cases. Birth weight, length, and body mass index of these children are 15-20% lower than those of their unaffected siblings (although often still in the normal range), a difference that indicates that growth is abnormal in the prenatal period. Prenatal hypotonia usually results in decreased fetal movement, increased incidence of abnormal fetal position, and the need for assistance during vaginal delivery or cesarean[9].

Because the diagnosis is typically established after the onset of obesity, it is important to consider requesting genetic testing for neonates and infants with hypotonia, feeding (suckling) difficulty, and some of the phenotypic features of the syndrome. This testing may contribute to an early diagnosis, thus reducing the use of invasive resources that are often difficult to interpret, such as electromyography and muscle biopsy[1].

In these cases, the most common cause of obesity is genetics, which is difficult to control. Therefore, the patient may exhibit long-term cardiovascular system disorders (hypertension, thrombophlebitis, chronic lower limb edema, early atherosclerosis), type II *diabetes mellitus*, in addition to sleep apnea, and cardiorespiratory failure[10]. The patient in question developed respiratory failure following lung infection

and had syndrome-associated comorbidities as aggravating factors.

Individuals with PWS have significant respiratory disorders, including central and obstructive sleep apnea, abnormal excitement, changes in circadian rhythm during REM sleep with reduced latency, abnormal response to hypercapnia, and excessive daytime sleepiness[3,8].

Central hypoventilation typically causes problems with daytime sleepiness and, if significant, may trigger pulmonary hypertension. Individuals with PWS are at risk of developing these problems due to decreased muscle tone, excessive obesity, and potential decreased neural activation for breathing. This case report shows that, after the child experienced ARDS, normalization of respiratory parameters was difficult. Obesity and decreased muscle tone were complicating factors. The patient remained on prolonged MV[11].

Obstructive sleep apnea is known to occur in 50-100% of cases of PWS, as well as in other syndromes with hypotonia, such as Down syndrome. It occurs when airflow into the lungs is hindered from airway obstruction, which leads to alveolar hypoventilation. These individuals usually exhibit wheezing and rhonchi associated with periods of calm, during which no air movement is noticed. Untreated obstructive apnea can have serious complications, including death[11,12].

Therefore, the pathogenesis of respiratory problems in PWS appears to be multifactorial in origin and goes beyond muscular hypotonia, which also contributes to the disorder by changing respiratory control, with low response to elevated CO_2 (hypoventilation), kyphoscoliosis (15%), and reduced diameter of the upper airways. The latter causes obstruction either through facial dysmorphism (such as retrognathia) and /or tonsillar hyperplasia, among other causes[12].

Other problems associated with breathing difficulties in the patient are chronic gastric reflux and aspiration. Reflux should be investigated in children with chronic respiratory problems, especially those with obstructive sleep apnea[11].

Cases of pulmonary infection due to reflux and bronchopulmonary aspiration are common, and these cases are explained by the pathophysiology and associated factors. Identifying the possible etiologies aids in the adequate use of antibiotics.

Unfortunately, no drug or surgical treatment has been found to be effective in the long term. The prevention of obesity and its complications is one of the biggest challenges of this syndrome; rigorous diet control and early physical activity are encouraged. The use of growth hormone (GH) has been shown to be beneficial, but is still controversial[6].

Due to concerns over sudden death from worsened respiratory obstruction (at the beginning of growth and after treatment with GH), Eiholzer et al.[4,11] proposed the use of polysomnography and an assessment to determine the presence of enlarged tonsils and adenoids before and after 6 to 12 weeks of its initiation.

Given the complexity of factors involved in PWS, from physical abnormalities to mental changes, a multidisciplinary monitoring plan should be proposed for the well-being of the patients and their families. Immunization programs should also be included in order to prevent major complications from respiratory infections.

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