

Caso Clínico

Clinical Case

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Infecção por *Bordetella pertussis* com hipertensão pulmonar grave num recém-nascido com boa evolução clínica – Caso clínico

Pertussis with severe pulmonary hypertension in a newborn with good outcome – case report

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Resumo

Apesar da ampla cobertura vacinal, a infecção por *Bordetella pertussis* está longe de estar controlada. Os recém-nascidos e lactentes ainda sem imunização completa e filhos de mães com baixos títulos de anticorpos para a *Bordetella pertussis* são altamente susceptíveis à infecção e têm maior risco de doença grave e morte. A infecção por *Bordetella pertussis* associada a hipertensão pulmonar no recém-nascido é frequentemente fatal.

Abstract

In spite of the availability and widespread use of vaccines, pertussis is far from controlled. Newborns and infants too young to be fully vaccinated, born from mothers with low antibody titers to *Bordetella pertussis*, are highly susceptible to infection and at risk of severe disease and death. Pertussis associated with pulmonary hypertension in the newborn is often fatal. The authors report a clinical case of severe

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Os autores descrevem um caso clínico de doença grave num recém-nascido com insuficiência respiratória aguda e hipertensão pulmonar grave, tratado com sucesso com sildenafil e óxido nítrico inalado.

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Palavras-chave: Recém-nascido, óxido nítrico, *pertussis*, hipertensão pulmonar, sildenafil.

pertussis-induced respiratory failure associated to severe pulmonary hypertension in a neonate successfully treated with sildenafil and inhaled nitric oxide.

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Key-words: Neonate, nitric oxide, pertussis, pulmonary hypertension, sildenafil.

Introduction

In spite of the availability and widespread use of vaccines, pertussis is far from controlled¹⁻³. Newborns and infants too young to be fully vaccinated are highly susceptible to infection and are at high risk of severe disease and death^{1,4,5}. Infants with pertussis may indicate undetected source cases in the community⁶. Clinical presentation of pertussis in the newborn may lack some features typical of the disease in older children¹. The characteristic “whoop” and fever may be absent¹. The clinical picture of the most severely affected newborns may be dominated by marked respiratory distress, cyanosis, and apnea¹. Pertussis associated with pulmonary hypertension in the newborn is often irreversible and associated to a poor outcome^{2,6-8}. The authors report a clinical case of severe pertussis-induced respiratory failure associated to severe pulmonary hypertension in a neonate with good outcome.

Case report

A 6 day-old white male infant born at term by caesarean section to a healthy, 38 year-

old, gravida II, para 0 mother, following a normal pregnancy, developed cyanotic episodes with no other associated symptoms at presentation. The mother denied infectious exposures.

He was admitted to the neonatal intensive care unit (NICU). He was afebrile, tachypneic, and presented labial cyanosis with crying. The resting transcutaneous oxygen saturation was 98%. The white blood cell count was $9.9 \times 10^9/L$ (62% lymphocytes) and the reactive C protein was 0.72 mg/dl. The chest X-ray revealed diffuse bilateral pulmonary infiltrates (figure 1). The echocardiographic evaluation revealed a structurally normal heart and severe pulmonary hypertension. Intravenous ampicillin and gentamicin were initiated.

Three hours after NICU admission he developed severe respiratory distress with progressive respiratory failure, requiring tracheal intubation and respiratory support with increasing ventilation parameters [maximal peak inspiratory pressure (PIP) 30 cmH₂O, rate 70/min, and FiO₂ = 1]. The oxygenation index was > 20 (OI = mean airway

pressure $\times \text{FiO}_2 \times 100 / \text{PaO}_2$). There was no improvement in pulmonary status after a trial of exogenous surfactant. Inhaled nitric oxide (iNO 20 ppm) was initiated 40 hours after admission.

At day three, inotropic support with dopamine was required. The pulmonary hypertension remained severe (estimated pulmonary artery pressure > 100 mmHg) and treatment with sildenafil was initiated (0.25 mg/kg in the first day, followed by 0.25 mg/kg/day increments until a total dose of 2 mg/kg, via orogastric tube).

At day six, estimated pulmonary artery pressure was about 70 mmHg, oxygenation index was below 20, and weaning of iNO was started with a decrease of 2 ppm every four hours. iNO was used for a total of five days. From day two to day three iNO was used in association to increasing doses of sildenafil. Blood cultures were negative as were rapid diagnostic testing for respiratory virus in nasopharyngeal aspirate. The initial work-up included a nasopharyngeal wash fluid culture and polymerase chain reaction (PCR) for *Bordetella pertussis* (Properatus Real Time-Prodesse, Waukesha, WI, USA). The PCR was positive so the patient started a full course of erythromycin. Antibody titers to *Bordetella pertussis* were not elevated. The family evaluation revealed that a three years old brother presented a flu-like syndrome with mild cough during the previous days, but no further cases of respiratory infection were disclosed in close relatives. All family members were treated with erythromycin. Laboratory evaluation of the brother was not performed.

The child's pulmonary vascular pressures and respiratory status improved gradually over the next days. Sildenafil was weaned

from day 17 to day 24. He was extubated 18 days after NICU admission, and discharged six days later.

At six months of age the child is asymptomatic and presents a good development.

Discussion

Pertussis is a highly contagious respiratory bacterial infection caused by *Bordetella pertussis*, a Gram-negative bacillus⁴. In spite of widespread immunization, pertussis occurs in exposed and unprotected newborns¹⁻³ and remains one of the most common causes of death from infectious diseases worldwide^{3,4}. Older children or adults in the household with undiagnosed mild disease are the usual sources of infection for neonates^{1,3,9,10}. In 1997, almost 24% of the notified cases in the United States occurred



Fig. 1 – The chest X-ray at admission revealed diffuse pulmonary infiltrates predominant in the upper 2/3 of both pulmonary fields

in infants less than six months age, including 18% in less than three months^{10,11}. According to a study by Wendelboe AM *et al*, household members are responsible for 76% – 83% of transmission of *Bordetella pertussis* to infants¹². Pertussis in infants less than one year of age should be considered as an indicator of undetected disease in the community⁶.

Mortality due to pertussis usually results from secondary pneumonia, encephalopathy, cardiac failure, or pulmonary hypertension^{1,7}. Most deaths occur among unvaccinated children or children too young to be vaccinated⁵. Patients younger than six weeks present the highest mortality⁴. Almost all cases of pertussis in the neonate associated with pulmonary hypertension reported in the international literature were fatal^{2,6-8}.

Antibody to *Bordetella pertussis* crosses the placenta and titers in immune mothers and their newborns are approximately equal¹. High titers of passively transferred antibody are protective for the newborn¹. Many women vaccinated during infancy present low serum levels of antibody when they reach childbearing age. These levels of antibody may be insufficient to protect the offspring, if they are exposed to pertussis during the first few months of life¹. We did not evaluate the mother's titers of antibody, but we believe that they were insufficient for the newborn's protection.

No serological test (IgG and IgA) is diagnostic for *Bordetella pertussis* infection in spite of the widespread and heterogeneous stimulated immunological response, differing between individuals according to age and previous exposure to microorganism or vaccine¹⁰. Our patient was in an immun-

nized and immunocompromised state as result of his age, and this may be the explanation for the low titers of antibodies.

Although not specific, elevation of white blood cells and lymphocytosis are common findings in the classic *Bordetella pertussis* infection¹⁰.

When newborns or infants present with unexplained pulmonary hypertension and respiratory failure, the diagnosis of pertussis should be investigated⁴. The standard approach to the diagnosis of pertussis include a nasopharyngeal wash culture, direct fluorescent antibody, serology and polymerase chain reaction^{1,4}. It is helpful to inform the laboratory of the suspicion because a specialized agar medium (Regan-Lowe or Bordet-Gengou) is required¹. This may be the reason why the cultures performed were negative in this case report. Anyway, with special culture mediums the incubation period lasts about 10-14 days.

PCR for *Bordetella pertussis* is a useful tool for pertussis diagnosis, particularly in pre-vaccinated infants^{13,14}. The new molecular assay proved to be suitable for the rapid diagnosis of pertussis in the routine diagnostic laboratory¹⁵⁻¹⁸. PCR positive results may be obtained at least 21 days after the onset of clinical symptoms¹⁹. PCR was the only positive marker of infection in this case report. Whether one single positive value of PCR is enough for the diagnosis is a question that, in this particular case, could only be answered by the apparent response to treatment with erythromycin.

iNO is a selective pulmonary vasodilator without significant effects on the systemic circulation. It causes vasodilation by acting on the receptors in the muscle wall of the blood vessels. Guanylyl cyclase activation

leads to production of cyclic guanosine monophosphate (GMP) and subsequent smooth muscle relaxation, the same mechanism of endogenous NO. Excess iNO is quickly bound to and inactivated, producing methemoglobin. The half-life is less than five seconds, and it is usually given continuously as a gas by inhalation. Sildenafil is selective phosphodiesterase (PDE5) inhibitor. This inhibition leads to accumulation of cyclic GMP in pulmonary smooth muscle cells, causing pulmonary vascular relaxation, and it may potentiate the effect of iNO. The association of sildenafil may also help on the gradual weaning of iNO. Data on sildenafil use in neonates are very limited. The most concerning short term adverse effects are worsening oxygenation and systemic hypotension, occurring mainly in patients with sepsis. A case of severe retinopathy of prematurity has also been described²⁰.

The early echocardiographic evaluation was important for the diagnosis of pulmonary hypertension. The prompt treatment with iNO and the association of sildenafil were successful in this case, and up to our knowledge were never reported in the literature in similar situations. Our case supports the idea that the immediate diagnosis and treatment of pulmonary hypertension in the course of the pertussis disease are important measures for the success of treatment.

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