CASE REPORT

Encephalopathy: A Rare Complication of an Infection by *Bordetella pertussis*

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Abstract

Newborn, 25-day-old admitted for paroxysmal cough, moaning, bilateral crackling with apnoea and acute respiratory failure. Chest X-ray showed an infiltrate in the left hemithorax. Blood tests showed 38,000/µL leukocytes, 19,000/µL lymphocytes and C-reactive protein of 27.4 mg/L. The patient was started on cefuroxime and gentamicin and needed mechanical ventilation. Polymerase chain reaction for *Bordetella pertussis* was positive and azithromycin was associated. He did not undergo exchange transfusion. On the third day, the newborn initiated clonic movements of the limbs. The electroencephalogram showed epileptiform activity in the posterior temporal regions. The cerebrospinal fluid had 40 cells/µL and 254 mg/dL proteins, and the magnetic resonance showed hyperintensity of the frontoparietal white matter and thalamus. Evolution was favourable under phenobarbital and phenytoin. Within the family, which was a supporter of the antivaccine movements, no family member was vaccinated. *Pertussis* encephalopathy is a rare but feared complication of *Bordetella pertussis* infection. An exchange transfusion may improve the prognosis. Universal vaccination, particularly in pregnant women, is an important public health measure for the protection of vulnerable groups.

Keywords: Brain Diseases/aetiology; Brain Diseases/therapy; Bordetella pertussis; Infant, Newborn; Whooping Cough/complications; Whooping Cough/therapy

Introduction

Pertussis (whooping cough) remains a serious public health problem and is still endemic worldwide. In 2014, 24.1 million cases of infection and 160,700 deaths in children under the age of 5 years were estimated.[1] The disease remains active, with cycles every three to five years. In the United States, among multiple outbreaks, the last three were the greatest of the last 50 years.[2] In Portugal, the incidence of this disease has also increased.[3] Different methodologies for case definition, surveillance, reporting and laboratory diagnosis, different vaccine efficacy, progressive decrease in vaccinal immunity, emergence of other species of *Bordetella* (*Bordetella holmesii, Bordetella parapertussis* and *Bordetella bronchiseptica*), and genetic variability in *Bordetella pertussis* are factors involved in disease reappearance.[4,5]

In Portugal, pertussis has been a disease of compulsory notification since 1950. The vaccine was introduced in the national vaccination plan in 1965 and, in 2006, the whole-cell pertussis vaccine (wP), which is more reactogenic, was replaced by the acellular pertussis vaccine (aP). Vaccination coverage at 12 months and 5 years of age has remained at 95% for the last two decades.[3]

The disease is described in all age groups as vaccinal immunity decreases over the years. In adolescents and adults, the clinical course is usually benign, but small infants may experience serious complications in several organ systems.[6] The most frequent are respiratory (apnoea, pneumonia), cardiovascular (arrhythmias, bradycardia) and neurological (seizures and encephalopathy) complications.

Case Report

A male newborn, 25 days of age, born by normal vaginal delivery at 39 weeks gestation was admitted for paroxysmal cough and respiratory distress over the previous 72 hours. Auscultation showed bilateral wheezing and crackles. The chest X-ray showed an infiltrate in the left hemithorax. At admission, blood tests showed leukocytes of 38,000/µL, lymphocytes of 19,000/µL (50%), monocytes of 4,000/µL (11%) and C-reactive protein

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of 27.4 mg/L. Following a diagnosis of pneumonia, the newborn was treated with intravenous ampicillin, cefuroxime and gentamicin. After 12 hours, the patient experienced clinical worsening, with apnoea and acute respiratory failure, and volume-targeted synchronised intermittent positive pressure ventilation was introduced for three days.

None of the family members, who supported antivaccine movements, were vaccinated, and the newborn's mother and 5-year-old brother had a cough for two weeks. Due to a clinical and epidemiological suspicion of pertussis, a polymerase chain reaction for *Bordetella pertussis* in the respiratory secretions was requested, which was positive on the second day of hospitalisation. Consequently, azithromycin was administered for five days. The maximum value of leukocytes was 72,000/µL on the second day of hospitalisation, decreasing to 50,000/µL after 24 hours. For this reason, no exchange transfusion was performed.

On the third day of hospitalisation, the newborn began subtle clonic movements of the left upper limb. The electroencephalogram showed moderate epileptiform activity in the posterior temporal regions, in independent foci bilaterally, and therefore the patient received intravenous phenobarbital therapy. As the patient developed clonic episodes in all four limbs, none associated to cough, intravenous phenytoin was initiated. At examination the cerebrospinal fluid was clear, with 40 cells/uL, a predominance of polymorphonuclear cells, a cerebrospinal fluid glucose concentration of 52 mg/dL (capillary blood glucose of 123 mg/dL) and a cerebrospinal fluid protein concentration of 254 mg/dL. The cultural study was negative. The cranial magnetic resonance scan showed a T2 hyperintensity in the frontoparietal white matter, with a subtle identical hyperintensity in the medial aspect of the thalamus, with no evidence of diffusion restriction. The possibility of *Bordetella pertussis* encephalopathy was suggested. Evolution was favourable with the established therapy, with no new seizures, and the anticonvulsant therapy was kept for 10 days. At 18 months old, the psychomotor development was normal. From a respiratory point of view, the clinical evolution was also favourable. During hospitalisation, and at their request, the entire family was also vaccinated, and prophylaxis was given to epidemiological contacts.

Discussion

Encephalopathy is a rare complication of *Bordetella pertussis* infection (0.5%-1% of all cases). It is more frequent in children under the age of 2 years (1.4% under the age of 2 months, 0.9% up to the age of 12 months and 0.7% above the age of 1 year), without gender predominance, although it may also affect adults.[7] Due to its morbidity, it is one of the most feared complications of the disease. The clinical condition starts with seizures, as in the case of our patient, but also with sensory or motor focal deficits and/or progression to coma in more than 50% of patients. Surviving patients may have neurological sequelae and multiple development deficits.

The pathophysiology of *pertussis* encephalopathy has been widely debated since the bacterium has never been isolated in the cerebrospinal fluid of affected patients and its etiopathogenesis has not yet been clarified. Most often, as seen in this case, seizures arise in the second stage of the disease, also known asthe paroxysmal phase, but they are not temporally related to the episodes of hypoxia characteristic of the paroxysmal cough. As the concentration of bacteria is at the maximum level in the first stage of the disease or catarrhal stage, it is unlikely that toxins are the main etiological factor of the disease. The literature on this topic is scarce, but encephalopathy seems to be multi-factorial, a process in which toxins, products of bacterial lysis, hypoxemia, carbon dioxide retention and loss of vascular regulation in the central nervous system, probably lead to an increase in the permeability of the blood brain barrier to inflammatory factors.[8,9] Diagnosis is considered in the presence of seizures or other neurological symptoms in patients with confirmed infection by *Bordetella pertussis* and in the absence of another most likely diagnosis. As it is the case of our patient, the electroencephalogram confirmed epileptic activity in the absence of changes suggestive of infection in the cerebrospinal fluid, but with signs of inflammation, including an increase in cells and a high cerebrospinal fluid protein concentration. The cranial magnetic resonance scan showed nonspecific signs of inflammation, similar to other cases described in the literature.[10,11]

In this case, encephalopathy was associated with another complication, pneumonia, also with a high neonatal mortality.[12] Pneumonia often leads to acute respiratory failure with refractory hypoxemia secondary to pulmonary hypertension. These patients may rapidly progress to cardiogenic shock in the malignant *pertussis* syndrome. In these cases, mortality is high and may reach 75%.[12] Risk factors for this syndrome are: age under 6 months old, prematurity, absence of whole-cell pertussis vaccination and hyperleukocytosis.[13] In our case, the newborn'srisk factors were age, absence of vaccination and leukocytes of 72,000/µL. However,the patient did not progress to this syndrome. A reduction in leukocytes in a short period of time may have contributed to the absence of this complication.

Hyperleukocytosis is associated with a higher mortality by *Bordetella pertussis.*[14] The increase in the absolute number of leukocytes and the timing of leucocytosis onset are associated with a higher mortality risk, which may be decreased through an exchange transfusion.[15] In Portugal, there are no recommendations about this therapy, however, it should be considered early on, ideally before respiratory and/or heart function deterioration. The white blood cell count should be monitored until the total leukocyte count is below 50,000/µL. An exchange transfusion is recommended if leukocytes are above 100,000/µL with no complications, or above 70,000/µL with respiratory or heart failure with or without echocardiographic evidence of pulmonary hypertension.[15] An exchange transfusion decreases the number of leukocytes, aggregates of leukocytes and thrombus formation in the pulmonary vessels, improves oxygenation and prevents progression to cardiogenic shock. In addition, plasma exchange may decrease toxin circulation, which contributes to heart and lung damage.[15] The largest case series of severe pertussis, treated with leukoreduction, showed a reduction in mortality from 45% (4/9) to 10% (1/10)[16] and, therefore, recommendations for this technique should also be discussed in Portugal.

Currently, other therapies are being discussed. As the pulmonary capillary bed is relatively narrow, the deformability of the white blood cells explains the 10 to 15 times higher transit time compared to the red blood cells. This situation, associated with hyperleukocytosis, may explain the increased resistance to standard treatments of pulmonary hypertension, namely nitric oxide and extracorporeal membrane oxygenation.[15]

Neither the infection nor the vaccine confers permanent immunity. Consequently, in the last 20 years, there has been a change in the ages at which the disease is more frequent, changing from the group of children under the age of 10 years to teenagers, adults, small infants and newborns.[17] Taking into account that the risk of mortality is higher in infants under the age of 3 months, in 2017 the vaccination of pregnant women was introduced in the national vaccination programme, and should be administered between 20 and 36 weeks of gestation, ideally up to 32 weeks.[3] Maternal vaccinal antibodies transmitted transplacentally allow for the decrease of complications and mortality in one of the most vulnerable age groups.[17] Thus, in the future, vaccination of pregnant women on a large scale may also decrease the severe complications of the disease.

WHAT THIS CASE REPORT ADDS

- The spectrum of severity of pertussis.
- The challenges in the understanding of the pathophysiology of encephalopathy, a complication of a disease first described more than a 1000 years ago.
- The importance of exchange transfusion and its indications.
- The importance of vaccination in pregnant women.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

References

1. Yeung KH, Duclos P, Nelson EA, Hutubessy RC. An update of the global burden of pertussis in children younger than 5 years: a modelling study. Lancet Infect Dis 2017;17:974-80. doi: 10.1016/S1473-3099(17)30390-0.

2. Poland GA. Pertussis outbreaks and pertussis vaccines: New insights, new concerns, new recommendations? Vaccine 2012;30:6957-9. doi: 10.1016/j.vaccine.2012.09.084.

3. Direção Geral da Saúde. Vacinação da grávida contra a tosse convulsa. Orientation no. 002/2016 (15/07/2016). Lisboa: DGS; 2016.

4. Pittet LF, Emonet S, Schrenzel J, Siegrist CA, Posfay-Barbe KM. Bordetella holmesii: An under-recognised Bordetella species. Lancet Infect Dis 2014;14:510-9. doi: 10.1016/S1473-3099(14)70021-0.

5. Cherry JD. Why do pertussis vaccines fail? Pediatrics 2012;129:968-70. doi: 10.1542/peds.2011-2594.

6. Kilgore PE, Salim AM, Zervos MJ, Schmitt HJ. Pertussis: Microbiology, disease, treatment, and prevention. Clin Microbiol Rev 2016;29:449-86. doi: 10.1128/CMR.00083-15.

7. Grant CC, McKay EJ, Simpson A, Buckley D. Pertussis encephalopathy with high cerebrospinal fluid antibody titers to pertussis toxin and filamentous hemagglutinin. Pediatrics 1998;102:986-90. doi: 10.1542/peds.102.4.986.

8. Carbonetti NH. Pertussis toxin and adenylate cyclase toxin: Key virulence factors of Bordetella pertussis and cell biology tools. Future Microbiol 2010;5:455-69. doi: 10.2217/fmb.09.133.

9. Kugler S, Bocker K, Heusipp G, Greune L, Kim KS, Schmidt MA. Pertussis toxin transiently affects barrier integrity,

organelle organization and transmigration of monocytes in a human brain microvascular endothelial cell barrier model. Cell Microbiol 2007;9:619-32. doi: 10.1111/j.1462-5822.2006.00813.x.
10. Hiraiwa-Sofue A, Ito Y, Mori H, Ichiyama T, Okumura A. Pertussis-associated encephalitis/encephalopathy with marked demyelination in an unimmunized child. J Neurol Sci 2012;320:145-8. doi: 10.1016/j.jns.2012.06.010.
11. Chin L, Burgner D, Buttery J, Bryant P. Pertussis encephalopathy in an infant. Arch Dis Childhood 2013;98:163. doi: 10.1136/archdischild-2012-303069.
12. Sawal M, Cohen M, Irazuzta JE, Kumar R, Kirton C, Brundler MA, et al. Fulminant pertussis: A multi-center study with new insights into the clinical-pathological mechanisms. Pediatr Pulmonol 2009;44:970-80. doi: 10.1002/ppul.21082.
13. Winter K, Zipprich J, Harriman K, Murray EL, Gornbein J, Hammer SJ, et al. Risk factors associated with infant deaths from pertussis: A case-control study. Clin Infect Dis 2015;61:1099-106. doi: 10.1093/cid/civ472.
14. Pierce C, Klein N, Peters M. Is leukocytosis a predictor of mortality in severe pertussis infection? Intensive Care Med 2000;26:1512-4. doi: 10.1007/s001340000587.
15. Kuperman A, Hoffmann Y, Glikman D, Dabbah H, Zonis Z. Severe pertussis and hyperleukocytosis: Is it time to change for exchange? Transfusion 2014;54:1630-3. doi: 10.1111/trf.12519.
16. Rowlands HE, Goldman AP, Harrington K, Karimova A, Brierley J, Cross N, et al. Impact of rapid leukoreduction on the outcome of severe clinical pertussis in young infants. Pediatrics 2010;126:816-27. doi: 10.1542/peds.2009-2860.
17. Bechini A, Tiscione E, Boccalini S, Levi M, Bonanni P. Acellular pertussis vaccine use in risk groups (adolescents, pregnant women, newborns and health care workers): A review of evidences and recommendations. Vaccine 2012;30:5179-90. doi: 10.1016/j.vaccine.2012.06.005.

Encefalopatia: Uma Complicação Rara de Infeção por Bordetella pertussis

Resumo:
Recém-nascido com 25 dias de vida internado por tosse acessual, gemido, fervores crepitantes bilaterais, apneia e insuficiência respiratória aguda. Na admissão, a radiografia do tórax apresentava hipotransparência no hemitórax esquerdo e analiticamente tinha leucocitose 38 000/mL, linfocitose 19 000/mL e proteína C reativa 27,4 mg/L. Iniciou ampicilina, cefuroxime e gentamicina e ventilação mecânica. A reação em cadeia da polimerase para *Bordetella pertussis* foi positiva e associou-se azitromicina, mas não realizou técnicas de leucorredução. Ao terceiro dia iniciou movimentos subtis clónicos dos membros. O eletroencefalograma apresentava atividade epileptiforme nas regiões temporais posteriores. Líquido cefalorraquidiano com 40 células/µL com predomínio de polimorfonucleares, glicorraquia normal e proteinorraquia 254 mg/dL. A ressonância magnética crânio-encefálica em T2 revelou hipersinal da substância branca frontoparietal e tálamos. A evolução clínica foi favorável sob fenobarbital e fenitoina. Na família, simpatizante de movimentos antivacinas, nenhum elemento estava vacinado.
A encefalopatia da *pertussis* é uma complicação rara e a exsanguineotransfusão pode melhorar o prognóstico. A vacinação universal é uma importante medida de saúde pública em especial na grávida para a proteção dos grupos vulneráveis.

Palavras-Chave: Bordetella pertussis; Coqueluche/complicações; Coqueluche/terapia; Encefalopatias/etiologia; Encefalopatias/terapia; Recém-Nascido