DIFFICULT MANAGEMENT OF PEDIATRIC ACUTE Q FEVER

FEBRE Q PEDIÁTRICA. UM CASO DE DIFÍCIL ABORDAGEM

Rafael Costa Figueiredo1, Diana R. Monteiro2, Ana Isabel Rebelo2, Ana Azevedo2, Sara Freitas de Oliveira2, Susana Tavares2

ABSTRACT

Introduction: Q fever, a zoonosis caused by *Coxiella burnetii*, is relatively rare in the pediatric population. The disease is often asymptomatic or with mild clinical presentation in children.

Case report: A four-year-old boy with persistent fever, severe anemia, and positive IgM for *Coxiella burnetii* was treated with trimethoprim-sulfamethoxazole and azithromycin, with no improvement. After polymerase chain reaction confirmation, he completed 14 days of doxycycline, with good response. After eleven months, the child remains asymptomatic.

Discussion: Despite having a usually mild presentation, the severe clinical progression and lack of response to initial antibiotic therapy in this case prompt the use of doxycycline, a non-consensual drug in younger ages, with good results. New recommendations endorse the use of this drug for short periods at any age.

Keywords: acute Q fever; doxycycline; pediatric Q fever

RESUMO

Introdução: A febre Q, uma zoonose causada por *Coxiella burnetii*, é relativamente rara em idade pediátrica. Em crianças, a doença é frequentemente assintomática ou com apresentação clínica ligeira.

Caso clínico: Uma criança do sexo masculino de quatro anos de idade com febre persistente, anemia grave e IgM positiva para *Coxiella burnetii* foi medicada com trimetoprim-sulfametoxazol e azitromicina, sem melhoria. Após confirmação da infeção por polymerase chain reaction, completou 14 dias de doxiciclina, com boa resposta. Onze meses depois, a criança permanece assintomática, sem sinais de doença.

Discussão: Apesar de ser habitualmente uma doença ligeira, a evolução clínica grave e falta de resposta à antibióterapia inicialmente instituída neste caso levaram à utilização de doxiciclina, um fármaco não consensual em idades mais jovens, com bons resultados. Novas recomendações sustentam o uso de doxiciclina por curtos períodos em todas as faixas etárias.

Palavras-chave: doxiciclina; febre Q aguda; febre Q pediátrica
INTRODUCTION

Q fever is a zoonosis caused by Coxiella burnetti (CB), an intracellular gram-negative coccobicillus first described in 1937 in Queensland, Australia. It has worldwide distribution and lower incidence in the pediatric compared to the general population, although it is probably underestimated.1-4

The natural CB reservoirs are herbivorous animals, such as bovines, goats, and sheep, but infection of other domestic or wild animals is also possible. Transmission is usually through inhalation but may also occur through ingestion of contaminated animal products, ticks, or contact with infected humans.1-4

The likelihood of asymptomatic disease is higher in the pediatric than in the adult population, presenting with mild clinical course.1-2 Manifestations are usually nonspecific and include fever, headache, weakness, cough, and other systemic symptoms. Gastrointestinal manifestations, such as diarrhea, vomiting, and abdominal pain, and nonspecific rash may also be present. Hepatosplenomegaly is frequent. The disease may also manifest as pneumonia, hepatitis, myocarditis, pericarditis, encephalitis, meningitis, hemolytic uremic syndrome, hemophagocytic syndrome, lymphadenitis, cholecystitis, and rhabdomyolysis. It lasts a few weeks and is often self-limited.1-3,5

Analytically, an increase in liver enzymes is usually observed. Hyperbilirubinemia and leukocytosis may occur, although a normal leucogram is frequent. In the initial phase, thrombocytopenia can be observed, with subsequent thrombocytosis and increased sedimentation rate and C-reactive protein.1-3,5

The diagnosis of acute infection is based on seroconversion, detection of CB DNA by polymerase chain reaction (PCR) or immunohistochemistry in patient samples or culture.1-4 Progression to chronic disease may occur, manifesting as recurrent or multifocal osteomyelitis, endocarditis, or chronic hepatitis, but has been rarely reported in children.1-2,5

CLINICAL CASE

A previously healthy four-year-old boy living in a rural environment with goats in the neighborhood, house with basic sanitation, drinking water from a well, and occasionally contacting a vaccinated dog was observed in the Emergency Department with a history of fever with ten days of evolution and no other symptoms. No history of ingestion of unpasteurized dairy food, medication, recent trips, or sick co-inhabitants was reported. The child had a good general appearance, pale mucosae, was anicteric, and presented palpable bilateral cervical lymph nodes (approximately 1.5 cm of greatest diameter) and axillary and inguinal millimetric lymph nodes. Abdomen examination revealed a palpable spleen 1 cm below the costal border at the midclavicular line, with no other changes.

Analytically, the boy presented with normocytic normochromic anemia (hemoglobin 7 g/dL), normal leucocyte, ferritin, and triglyceride values, slightly elevated transaminases (64 U/L AST, 40 U/L ALT), and elevated C-reactive protein (138.9 mg/L) and sedimentation rate (77 mm/h). Chest X-ray was normal, and abdominal ultrasound confirmed splenomegaly (bipolar diameter of 10.5 cm), with no other changes.

The patient was hospitalized with antipyretic therapy only. Serological tests for Epstein-Barr virus and cytomegalovirus and blood, urine, and stool cultures were negative. On the 17th day of fever onset, the abdominal ultrasound revealed homogenous hepatosplenomegaly, with a liver maximum longitudinal diameter of 12.5 cm and splenic bipolar diameter remaining at 10.4 cm.

Due to lack of improvement, workup was extended to include autoimmunity and auto-inflammatory markers, serology for parvovirus B19, herpes virus 1 and 2, human immunodeficiency virus, hepatitis A, B, and C virus, Mycoplasma pneumoniae, Toxoplasma gondii, various zoonosis (Rickettsia conorii, R. rickettsia, R. typhi, Borrelia burgdorferi, Bartonella henselae, Leishmania spp, Coxiella burnetti, Leptospira interrogans, Francisella tularensis), testing for Mycobacterium tuberculosis infection and screening for respiratory virus in nasopharyngeal secretions (which were only positive for influenza B virus). Echocardiogram revealed no cardiac involvement or endocarditis, lumbar puncture showed normal cerebrospinal fluid cytochemistry, and virologic and cultural exams were negative.

On D21 of fever, IgM (phase II) for CB came back positive (17 UA for a normal <11) despite negative IgG phase I and II, and treatment for Q fever with trimethoprim-sulfamethoxazole 12mg/kg/day IV was started. The patient was apyrexial between D27 and D30, at which point fever reinitiated. Azithromycin 10mg/kg/day IV was added for three days. Macular exanthema that disappeared upon digital pressure was evident on the trunk and face, without palmpomlar involvement. Abdominal and cardiac ultrasound reevaluation showed no changes.

Due to persistent fever, the patient was transferred to an Oncology hospital for assessment. Myelogram was normal, but worsening anemia (Hb 5.5 g/dl) prompted red blood cell transfusion.

On D36 of fever, blood PCR was positive for CB, and the patient was started on oral doxycycline 4.5 mg/kg/day. Before starting doxycycline, increased transaminases (142 U/L AST, 155 U/L ALT) were noticed, with progressive normalization. Two days after starting doxycycline, fever had resolved. The patient completed 14 days of doxycycline treatment without complications and with normalization of inflammatory parameters.

In reassessments, one and eight months after hospitalization, the boy was clinically well and had a normal physical exam. Two and nine months after the first serologies, IgM and IgG (I and II) reevaluations for CB were negative, showing no seroconversion. PCR was not repeated, and no further immunological evaluation was conducted. Cardiac ultrasound performed 11 months after the first evaluation remained unaltered.

Although a detailed public health department assessment was
DISCUSSION

Q fever in pediatric age is rare, with most studies reporting infection in active adult males. In Portugal, Q fever was first recognized in the mid-20th century and its notification became mandatory in 1999. The estimated incidence in 2008 was 0.11 per 10^5 inhabitants. The most recent large study in Portugal reported 247 cases of Q fever between 2004 and 2013, only two of which corresponding to pediatric patients. The Portuguese national surveillance system reported 96 cases between 2012 and 2015, six of which under 24 years of age. Seropositivity in children is significantly lower than in adults due to lower exposure risk and probable immune response differences.

Bacteria display antigenic phase variation, with phase I variant being highly infectious and phase II variant being avirulent and associated with acute infection. Protective antibodies against CB are directed primarily against phase I antigen. IgG antibody titer may confirm the diagnosis, but IgM positivity alone is not a diagnostic criterion, since IgM antibodies have lower specificity than IgG and may present cross-reactivity. Therefore, PCR positivity for CB was crucial for this patient’s diagnosis. Seroconversion allows only a retrospective diagnosis evidenced by a phase II IgG antibody titer rise between acute and convalescent samples. Antigenic phase variation and time from infection onset need to be taken into account when interpreting serology results, considering different cut-off values for acute and chronic infection in each assay. Despite initial positive phase II IgM serology, no seroconversion was observed in the patient. Lack of an adequate immune response should be considered in this patient, and an evaluation for primary immunodeficiencies should be conducted.

Treatment absence can be considered in cases of mild disease, given the usually favorable course. However, an infection with persistent severe clinical symptoms was observed in the present case (fever for over 38 days complicated by anemia requiring transfusion and mild hepatitis), making antibiotic therapy mandatory. In children under eight years, treatment with trimethoprim-sulfamethoxazole is appropriate. Due to diagnosis confirmation through PCR and lack of improvement, doxycycline was started, with favorable outcomes. This represents the first-line antibiotic therapy in adults and children over eight years of age. Some clinicians are reluctant to use it at younger ages due to the risk of tooth discoloration by incorporating tetracyclines into dental enamel. However, doxycycline binds less readily to calcium than other tetracycline class members, and in the past years, studies with children under eight years treated with short-term courses of doxycycline showed no differences in dental staining, enamel hypoplasia, or tooth coloring. The latest Report of the Committee on Infectious Diseases of the American Academy of Pediatrics endorses the use of doxycycline for up to 21 days in children of all ages.

Severe and chronic disease is associated with pre-existing morbidities, like cardiac and vascular malformations or presence of prosthesis. Although the present patient was previously healthy, the possibility of progression to persistent Q fever is real, and post-acute reassessment is always required. Laboratory revaluation should be performed six months after an acute infection diagnosis. In cases with associated risk factors, additional tests may be recommended. Regarding epidemiology, the only known possible transmission source in this case was goats in the patient’s neighborhood, which represent a natural CB reservoir. Veterinary assessment is mandatory to prevent inoculation of other individuals.

REFERENCES


CORRESPONDENCE TO
Rafael Costa Figueiredo
Department of Pediatrics
Centro Materno-Infantil do Norte
Centro Hospitalar Universitário do Porto
Largo da Maternidade de Júlio Dinis 45
4050-651 Porto
Email: rafaelcostafigueiredo@gmail.com

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