

Case Report

Beware of Temperature Changes: A Case Report of Paroxysmal Cold Haemoglobinuria

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Abstract

Paroxysmal cold haemoglobinuria is an immune haemolytic syndrome characterized by the presence of autoantibodies reactive against specific red blood cell antigens. At low temperatures, these antibodies and the complement fix to the red blood cells, leading to haemolysis upon warming up.

We present the case of a twenty-one months old male child, who presented with a six-day history of malaise, productive cough and fever, already medicated with amoxicillin and clavulanic acid two days before. On physical examination, the child was prostrated, severely pale, but with no hemodynamic instability or difficulty breathing. Blood tests revealed the presence of severe anaemia (Hb 5.4 g/dL), leucocytosis ($19.90 \times 10^9/L$), without immature cells in the blood film; reticulocytosis ($89.7 \times 10^9/L$) and evidence of hemolysis (haptoglobin

bin <8 mg/dL; LDH 1328 UI/L; bilirubin 1 mg/dL and unconjugated bilirubin 0.6 mg/dL), C-reactive-protein 56.7 mg/L. He received a transfusion of red blood cells, initiated treatment with oral clarithromycin and reinforced the rewarming of the extremities with good results (Hb 9.6 g/dL). Regarding serological investigation, the results revealed a positive IgM for *Mycoplasma pneumoniae*; positive Direct Antiglobulin Test with specificity for CD3, and positive Donath Landsteiner test, leading to the diagnosis.

This case report represents a syndrome that even though rare, is important to bear in mind when facing a case of severe haemolysis. Despite the favorable outcome, additional follow-up must be placed in outpatient setting, with periodic clinical and laboratorial reevaluations.

Keywords: Cold; Donath landsteiner; Haemoglobinuria; Mycoplasma pneumonia

Abbreviations

CMV: Cytomegalovirus
CRP: C-Reactive Protein
C3d: Complement 3d
DCT: Direct Coombs Test
EBV: Epstein-Barr Virus
Hb: Hemoglobin
Htc: Hematocrit
ICT: Indirect Coombs Test
IgG: Immunoglobulin G
IgM: Immunoglobulin M
LDH: Lactate Dehydrogenase
L: Lymphocytes
MGV: Mean Globular Volume
N: Neutrophils
PCH: Paroxysmal Cold Haemoglobinuria
RBC: Red Blood Cells

Introduction

Paroxysmal Cold Haemoglobinuria (PCH) is a rare form of auto-immune haemolytic anaemia. It is characterized by the presence of IgG autoantibodies that bind to the P antigen on the Red Blood Cell (RBC) surface [1-5] sensitizing the RBCs by fixing complement. This occurs in the extremities at colder temperatures [5], and upon circulation on warmer parts of the body, there is activation of the complement cascade resulting in intravascular haemolysis and haemoglobinuria [1,4,5].

Despite being a disease that might appear at any age, it is more common among the paediatric age group [1,4,6]. Most cases are seen in children under 5 years of age, with male predominance [5]. According to European epidemiologic studies, even though populational data are limited, its estimated prevalence varies between 1.6 % and 40 % of all autoimmune haemolytic anaemia episodes [4,5]. The recent raise in its incidence could be due to an increase in the awareness of the disease and of the Donath-Landsteiner Test [3].

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This syndrome usually appears within 7-10 days after an infection and may persist for 6-12 weeks after its resolution [1]. Severe anemia, pallor, haemoglobinuria, presence of intravascular haemolysis, without hepatosplenomegaly are typical manifestations of this syndrome [1-6]. Usually there is a significant improvement just with supportive measures, RBC transfusion and antibiotics when there is a bacterial underlying infection, with no need to use corticosteroids or immunosuppressive drugs, as seen in the case presented.

Case Report

A twenty-one months old caucasian male child was admitted with a 6-day-history of fever (maximum temperature of 40°C, with 3-4 peeks per day, unresponsive to antipyretics), malaise, productive cough, vomiting and diarrhea. He had no relevant family or personal history, with no known anaemias; and no recent consumption of fava beans or any type of drugs. He was medicated with amoxicillin and clavulanic acid two days before for an upper respiratory infection (acute tonsillitis).

On physical examination, the child was prostrated, hemodynamically stable (arterial pressure: 97/53 mmHg; cardiac frequency: 128 bpm, capillary reperfusion time <2 s) and without respiratory distress signs. He was severely pale, hydrated but without jaundice. He also had bilateral tympanic membrane hyperaemia and tonsillar hypertrophy with purulent exudate. There were no further changes in the physical examination, namely: No palpable organomegaly, lymphadenopathies or macroscopic changes in urine. Blood tests revealed the presence of severe microcytic and hypochromic anaemia (Hb 5.4 g/dL, Htc 15.9 %, MGV 82 fL), leucocytosis (19.90 x 10⁹/L with 44.7 % N; 44.6 % L), without immature or abnormal red cells in the peripheral blood smear and a C-Reactive Protein (CRP) 56.7 mg/L. There was evidence of haemolysis (reticulocytosis 89.7 x 10⁶/L, haptoglobin <8 mg/dL (30-200 mg/dl), Lactate Dehydrogenase (LDH) 1328 UI/L; bilirubin 1 mg/dL and unconjugated bilirubin 0.6 mg/dL).

After consulting the immunohemotherapy and paediatric haematology departments, other complementary exams were requested. The Direct Antiglobulin Test (Direct Coombs Test) was positive for Complement Component 3d (C3d) and the Indirect Antiglobulin Test (Indirect Coombs Test); was negative. The serologic tests revealed positive Immunoglobulin G (IgG) for Cytomegalovirus (CMV) and Epstein-Bar Virus (EBV) and positive Immunoglobulin M (IgM) for *Mycoplasma pneumoniae*. The final diagnosis of PCH was established by the previous results and a positive Donath-Landsteiner Test.

Upon admission, he received a transfusion of red blood cells (15 mL/Kg), with a good response—a rise in the haemoglobin level to 9 g/dL (post transfusion) and 9.9 g/dL at discharge (D6). Treatment with oral clarithromycin was initiated and some supportive measures were reinforced, such as rehydration, extremities rewarming and prevention of cold exposure. While admitted, he experienced progressive clinical and analytical improvement, with haemolysis resolution (reticulocytes 253 x 10⁶/L; bilirubin 0.40 mg/dL; unconjugated bilirubin 0.20 mg/dL; LDH 923 UI/L and haptoglobin 12 mg/dL).

After discharge, a follow-up appointment by a paediatric haematologist was made. At 2 months follow-up, the child remained without any recurrence of the symptoms, with haemoglobin levels of 12 g/dl, without reticulocytosis or any other evidence of haemolysis. The initial immunohematological tests were repeated, confirming the previously established diagnosis.

Conclusion

Faced with a case of a previously healthy child who develops severe acute anaemia accompanied by reticulocytosis, a haemolytic pattern and a normal peripheral blood smear, an autoimmune cause must be considered and a Coombs Test should be requested. Our patient's Direct Coombs Test showed monospecificity for C3d which is very suggestive of a cold agglutinin-mediated autoimmune haemolytic anemia.

The final diagnosis was possible through the Direct Coombs Test, that was positive to anti-C3 and negative to IgG [1,3-6]; and a positive Donath-Landsteiner Test, with addition of complement. This test revealed the acquired haemolytic anemia caused by biphasic IgG autoantibodies that sensitize RBCs at cold temperatures by fixing complement to the RBCs causing intravascular haemolysis upon rewarming [3,6]. This allowed the differential diagnosis with other diseases, such as Paroxysmal Nocturnal Haemoglobinuria and Cold Agglutinin Disease, that despite being clinically and analytically similar, have a different pathophysiology [3-5].

Nowadays, the PCH is more associated with viral infections and post-immunization status [1,4-6]. The most frequently associated agents are the measles, mumps, influenza, herpes, varicella, CMV, EBV, adenovirus, parvovirus B19, Coxsackie A9, *Haemophilus influenzae*, *Mycoplasma pneumoniae* and *Klebsiella pneumoniae* [4,5]. Other potential causes, although less frequent, are lymphoproliferative and other auto-immune diseases. In this case report, the PCH appears concurrent to an upper respiratory infection, a positive result of the serological test for *Mycoplasma pneumoniae* led us to consider this as the likely cause of this haematological syndrome.

The majority of the PCH episodes are acute and with spontaneous resolution within weeks, and just requiring some supportive and preventive measures [1,3,4]. Cold exposure should be avoided, hydration reinforced and attention to any sudden worsening of the child's well-being [1,4,5]. When facing a severe and symptomatic anaemia, warmed blood transfusion might be necessary [1,3], as in the case presented. Because most cases of acute PCH are transient and self-limited, there is usually no need for immunosuppressive or pharmacologic drug therapy [5]. A few studies have been performed to evaluate the role of corticosteroids in haemolysis's control, but the results were inconclusive [1,3-6]. On the other hand, the use of immunosuppressive drugs such as rituximab (an anti-CD20 monoclonal antibody) proved to be helpful in reverting haemolysis in refractory cases [5]. More recently, a new recombinant antibody-eculizumab has also been under investigation. Theoretically, for its inhibitory effect on the complement cascade, it seemed a promising drug, yet the results were rather disappointing [5]. Regardless of its favorable prognosis and rarely recurrent, a close clinical and analytical follow-up is essential in PCH, just has seen in the case presented.

This case report represents a syndrome that even though rare, is important to bear in mind when facing a case of severe haemolysis. It's a disease that generally has a benign course, being the knowledge of the diagnostic test and the avoidance of cold exposure the cornerstones for a fast and correct diagnosis, and determinant to recovery. Despite being self-limited and usually non-recurrent, sometimes severe presentations of this haemolytic syndrome might occur to which we should be aware.

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Conflict of interest

None of the authors have any relevant conflicts of interest to report.

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