

Case report:

Acute paroxysmal cold hemoglobinuria: A case report and literature review

Hasitha Gajaweera¹, Kavinda Dayasiri¹, Nayani Suraweera¹, Chandrachapa Gamage¹, Kumudu Weerasekara¹

Abstract:

Paroxysmal cold hemoglobinuria (PCH) is a very rare subtype of autoimmune hemolytic anemia caused by the presence of cold-reacting autoantibodies in the blood and characterized by the sudden presence of hemoglobinuria, typically after exposure to cold temperatures. The acute onset PCH occurs following viral illnesses whilst the chronic form is secondary to hematological malignancies and tertiary syphilis. It is a complement mediated intravascular hemolytic anemia associated with a biphasic antibody against the p antigen on red cells. We describe a three-year child who had acute onset PCH following likely viral infection. The diagnosis was confirmed by demonstration of strongly positive Donath Landsteiner antibodies. She made a gradual recovery with supportive treatment, ten days following the initial detection of hemolysis. Parents were educated about the need to avoid cold exposure to prevent precipitation of further hemolysis and folic acid was commenced to assist the recovery of erythropoiesis.

Keywords: paroxysmal cold hemoglobinuria, autoimmune hemolysis.

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Introduction

Paroxysmal cold hemoglobinuria (PCH) is a rare autoimmune hemolytic anemia mediated by a biphasic cold reactive IgG type autoantibody against p antigen on red blood cells. It triggers complement-mediated intravascular hemolysis¹ upon exposure to cold temperatures. It can occur abruptly in acute form following viral infections² and can be of chronic type secondary to hematological malignancies^{3, 4} and tertiary syphilis. The disease specific antibody known as “Donath Landsteiner” antibody was first described by Julius Donath and Karl Landsteiner⁵ and attaches to red cells at colder temperatures and causes red cell lysis when blood recirculates to warmer parts of the body. Common clinical manifestations include anemia and hemoglobinuria. PCH accounts for 2-10% of all autoimmune hemolytic anemias. The annual incidence of paroxysmal cold hemoglobinuria was estimated to be 0.4 cases per 100,000 population⁶. Herein, the authors describe

a child who had paroxysmal cold hemoglobinuria following a viral infection.

Case report

A three-year-old girl who was previously healthy and born to non-consanguineous parents from a low social background, presented with acute onset cola colour urine for one day duration. There had been a preceding history of upper respiratory tract infection 2 weeks before the onset of illness. Cola colour was more intense during early morning. There had been no history of exposure to cold climates or temperatures. Urine output was not reduced. The child did not have symptoms of anemia or heart failure on admission to the ward. There was no recent medication history. Further clinical evaluation did not reveal features of malignancy, infections or connective tissue disorders.

Examination revealed a pale and icteric child with adequate physical growth (weight – 10 kg, height – 94 cm). There was no lymphadenopathy,

1. Lady Ridgeway Children's Hospital, Colombo, Sri Lanka.

Correspondence to: Dr. Kavinda Dayasiri, MBBS MD M Phil FRCPCH, Consultant Pediatrician, Lady Ridgeway Children's hospital, Colombo, Sri Lanka. **E-mail:** kavindadayasiri@gmail.com

rashes, arthritis, oral ulcers, exudative tonsillitis or hepatosplenomegaly. Cardiovascular and respiratory systems were clinically normal. Table 1 shows sequential hematological indices and bilirubin over the course of illness.

Table 1. Variation of hematological indices and bilirubin over the course of illness

	1 week prior	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7
Hemoglobin (g/dl)	12.5	9.2	5.1	5.2	5.4	5.6	6
Platelets (x 10 ⁹)	333	390	360	347	348	323	325
Total Bilirubin (mg/dl)	-	129	127	172	131	53	34
Indirect Bilirubin (mg/dl)	-	86	104	146	103	43	26

Full blood count revealed normochromic normocytic anemia. Blood picture showed polychromatic cells, red cell agglutinins and erythrophagocytosis with evidence of cold autoimmune hemolytic anemia. Reticulocyte count was 0.8%. Liver functions were within normal limits (SGOT – 43 U/L, SGPT – 35). Serum creatinine was 28 µmol/l and blood urea were 7.3 mg/dl. Direct Coombs test was positive with C3d specificity. Epstein-Barr virus, Cytomegalovirus and Mycoplasma serology were negative. Urine analysis revealed hemoglobinuria and hemosiderinuria whilst hematuria was absent. Donath Landsteiner antibodies were strongly positive.

The child was managed with intravenous fluids, blood transfusions and warming with regular monitoring of hematological indices and serum bilirubin. She made a gradual recovery 10 days following the initial detection of hemolysis. Parents were educated about the need to avoid cold exposure to prevent precipitation of further hemolysis and folic acid was commenced to assist the recovery of erythropoiesis.

Discussion

Paroxysmal col hemoglobinuria is an autoimmune intravascular hemolytic anemia typically following exposure to cold temperatures.

However, occasionally a history of cold exposure may not be present⁷. Children are more susceptible for acute PCH presenting with a single, brief, post viral hemolytic episode⁸ although, recurrent episodes have been rarely reported⁹. Hemolysis is usually severe and rapidly progressive. It is often associated with a relative Reticulocytopenia suggesting an ineffective bone marrow response either due to marrow suppression from viral infection or other causes¹⁰.

PCH was first described as a distinct clinical entity in 1872¹¹. In the past, PCH was described predominantly following secondary and tertiary syphilis^{12, 13}. However, currently PCH is known to occur following viral illnesses, such as Epstein-Barr virus, mumps, measles, cytomegalovirus, coxsackievirus A9, influenza, chicken pox, parvovirus B19, and adenovirus^{14, 15, 16}. More commonly, a specific pathogen is not identified¹⁴. Rare examples of PCH have been described in patients with other immunologic disorders such as chronic lymphocytic leukemia¹⁷.

The reported symptoms include fever, abdominal pain, and constitutional symptoms that resolve spontaneously within a few days to several weeks after onset¹⁷. The antibody in PCH is a cold-reacting IgG. Unlike cold-reacting IgM, it does not cause red cell agglutination but, similar to cold-reacting IgM, it is able to fix complement readily. This results in intravascular hemolysis on rewarming. The maximum temperature at which these antibodies are able to interact varies greatly from patient to patient.

The diagnosis is established by demonstration of Donath-Landsteiner antibodies which is still considered the gold standard after it was first described in 1904¹⁸. The Donath Landsteiner antibody usually appears 1 week after the onset of illness and can be detected up to three months¹³.

Treatment is mainly supportive and includes red cell transfusions, intravenous fluids, and warming. Immunosuppressive therapy may be effective in severe cases. Most cases of acute PCH are acute, self-limiting disorders with a highly favorable prognosis although untreated children can develop complications following severe anemia.

Conclusion

This patient had a classic presentation of acute paroxysmal hemoglobinuria and made complete recovery upon timely supportive treatment. Whilst it is important to explore the underlying etiology with comprehensive evaluation, etiology may remain unknown in some cases.

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Ethical Approval: Written consent has been obtained from index patient's parents.

Authors Contribution: HG, KD, NS, CG participated in clinical management of the reported patient. KD performed literature survey, wrote and edited the manuscript. KW led clinical management and edited the manuscript. All authors approved the final version of the manuscript.

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