Case report

Acute paroxysmal cold haemoglobinuria; a case report and literature review

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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 Donnath Landsteiner antibodies. She made a gradual recovery with supportive treatment, ten days following the initial detection of haemolysis. Parents were educated about the need to avoid cold exposure to prevent precipitation of further haemolysis and folic acid was commenced to assist the recovery of erythropoiesis.

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Introduction

Paroxysmal cold hemoglobinuria (PCH) is a rare subtype of autoimmune hemolytic anemia characterized by presence of biphasic cold reactive IgG type autoantibodies against p antigen on red blood cells. These antibodies result in complement-mediated intravascular hemolysisfollowing exposure to cold temperatures and patient presents with acute onset heamoglobinuria. Whilst acute PCH can occur following viral infections and chronic PCH can present secondarily to chronic medical illnesses such as haematological malignancies, and tertiary syphilis. The cold reactive IgG antibody is also known as "Donnath Landsteiner" antibody which was first described by Julius Donath and Karl Landsteiner in medical literature. Donnath Landsteiner antibodies bind red blood cells at colder temperatures and antibody bound red blood cells undergo complement mediated haemolysis while circulating through warmer temperatures. The characteristic features of acute PCH include haemolytic anemia and haemoglobinuria.

Paroxysmal cold heamoglobinuria accounts for less than 1% of all autoimmune haemolytic anaemias,. The estimated annual incidence of PCH was 0.4 cases per 100,000 population in one study. Herein, the authors describe a child who had paroxysmal cold haemaglobinuria following a viral infection.

Case report

A three year old girl who was previously healthy and born to non-consanguineous parents from a low

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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, 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 haemolytic 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 was 7.3 mg/dl. Direct Coombs test was positive with C3d specificity. Epstein-Barr virus, Cytomegalo virus and Mycoplasma serology were negative. Urine analysis revealed haemoglobinuria and haemosiderinuria whilst haematuria was absent. Donnath 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 haemolysis. Parents were educated about the need to avoid cold exposure to prevent precipitation of further haemolysis and folic acid was commenced to assist the recovery of erythropoiesis.

Discussion

The first report of PCH as a syndrome of passage of red coloured urine upon exposure to cold was coined in 1872. PCH were described predominantly following secondary and tertiary syphyllis in the past, . Presently, PCH is known to follow a number of viral illnesses, such as parvovirus B19, Epstein-Barr virus, coxsackievirus A9, mumps, influenza, chicken pox, measles, cytomegalovirus, and adenovirus,,. However, a specific trigger is not identified in many children[14,16]. PCH have also been reported in patients with chronic lymphocytic leukemia.

Although acute onset haemolysis and haemoglobinuris in PCH occur following exposure to cold temperatures, occasionally a history of cold exposure may not be present. Children are more susceptible for acute PCH and can present with an isolated, short lasting, hemolytic episode following a viral infection.However, recurrent episodes of PCH in children have been reported[127]. Haemolysis is usually rapidly progressive and can be life threatening leading to severe anaemia. Reticulocyte count is often low for the degree of anaemia suggesting an inadequate bone marrow response due to marrow suppression from viral infection.

The clinical features of PCH include passage of red or brown coloured urine (heamoglobinuria), abdominal pain, headache, fever, malaise, fever with chills, and vomiting. Accumulation of bile pigments can rarely lead to acute kidney injury. IgM mediated cold autoimmune haemolytic anaemia is the main differential diagnosis.

The antibody in PCH is cold-reactive IgG. Although IgG antibodies do not cause red cell agglutination as seen with IgM, IgG bound red cells readily undergo complement mediated haemolysis. This leads to intravascular hemolysis in warm temperatures. The rate of haemolysis at different temperatures is variable in different patients.

The gold standard for diagnosis of PCH is demonstration of Donnath-Landsteiner antibodies. Donnath Landsteiner antibodies were first described in 1904. These antibodies usually appear 1 week after the onset of haemolysis and can be demonstrated up to three months.

Treatment is mainly supportive. Adequate hydration, pain relief and avoidance of cold form a key part of management. Red cell transfusions are indicated for patients with severe anaemia and acute warming helps in mitigating severe haemolysis. It is also important to monitor blood counts, reticulocyte count and if indicated, renal functions until complete recovery. Immunosuppressive therapy may be effective in severe cases. In most children with cute PCH, haemolysis is self-limiting and supportive care and monitoring are all that is required. However, untreated children can develop acute kidney injuryand complications following severe anemia.

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