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Acute Haemolytic Anaemia with a Positive Donath-Landsteiner Test Following Respiratory Syncytial Virus Infection

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Abstract We describe a case of paroxysmal cold haemaglobinuria (PCH) in a 23-month-old girl who presented with passage of dark urine, fever, chills and rigors six days after an episode of upper respiratory tract infection caused by respiratory syncytial virus. Paroxysmal cold haemaglobinuria is a rare form of autoimmune anaemia occurring in children. The diagnosis is confirmed by a positive Donath-Landsteiner test. The course of the haemolysis is usually self-limiting but the degree of anaemia thus caused can be severe. Treatment is symptomatic only and may involve blood transfusion if there is evidence of cardiopulmonary compromise.

Key words Donath-Landsteiner test; Haemolytic anaemia; Paroxysmal cold haemaglobinuria; Respiratory syncytial virus infection

Introduction

Paroxysmal cold haemoglobinuria (PCH) is a rare form of autoimmune haemolytic anaemia in children. It is characterized by the presence of a biphasic antibody known as the Donath-Landsteiner antibody. PCH is a recognized clinical entity in childhood usually occurring after an acute viral infection, although in earlier times it was often described as a complication of congenital syphilis. The presenting clinical feature is acute haemoglobinuria with passage of 'Coke-coloured' urine following exposure to 'cold'. The anaemia can be dramatic but the natural history of the illness is usually of brief duration without recurrence. We report a case of PCH probably precipitated by respiratory syncytial virus infection in a 23-month-old girl.

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Case Report

A 23-month-old girl was admitted to the Prince of Wales Hospital in July 2001 with symptoms of an upper respiratory tract infection. Respiratory syncytial virus (RSV) was isolated from the nasopharyngeal aspirate. She was managed with symptomatic treatment and antibiotics were not prescribed. She was discharged three days later after the fever subsided. She was apparently well until three days after discharge when she presented with gross painless 'haematuria' associated with recurrence of fever, chills, rigors and decreased appetite, and was readmitted into the hospital. Prior to the onset of these symptoms, she had been given herbs of unknown nature by the mother. There was no history of G6PD deficiency.

Physical examination on admission was unremarkable. Vital signs were as follows: temperature 36.1°C, respiratory rate 36/minute, blood pressure 78/49 mm Hg, pulse rate 124 beats per minute. There was no pallor or jaundice noticed. The liver and the spleen were not enlarged.

Initial investigations showed a haemoglobin level of 12.2 g/dl, white cell count 21.3 $x10^9$/l, (64% neutrophils, 33% lymphocytes, 1% monocytes, 2% eosinophils), platelet count 456$x10^9$/l, prothrombin time 11.4 seconds, activated

partial thromboplastin time 38.5 seconds, INR 1.13. Urine dipstick showed the presence of large amount of haemoglobin, but no red cells were seen under the microscope suggesting haemoglobinuria. Urine culture was negative. Liver and renal function test were normal except a raised total bilirubin of 49 umol/l (Direct bilirubin not checked). The potassium level could not be estimated as the blood sample appeared to be haemolysed.

The girl remained haemodynamically stable. The severity of haemoglobinuria improved after admission and subsided completely six days after the onset. However, she was noticed to have progressive pallor and jaundice. Haemoglobin dropped from 12.2 to 6.1 g/dl from day 1 to day 4 after admission. The MCV and MCH were 82.7 fL and 29.6 pg, respectively. Reticulocyte count was elevated to 5.9%. Blood smear showed marked spherocytosis, moderate anisocytosis, mild poikilocytosis and moderate polychromasia. Serum haptoglobin was <0.05 g/l (reference range: 0.33-1.71).

Direct Coombs' test was positive for polyspecific AHG and anti-C3d but negative for anti-IgG. Cold agglutinin titre with adult (I) cells, cord (i) cells and patient's cells was found to be negative. The Donath-Landsteiner test was positive confirming the diagnosis of paroxysmal cold haemoglobinuria. Anti-P antigen specificity was not investigated. Anti-nuclear factor was negative. Viral titres could not be performed on admission due to haemolysed specimen. Convalescent titres were less than 10 for adenovirus, influenza viruses, parainfluenza viruses and mycoplasma pneumoniae. The convalescent titre for respiratory syncytial virus was 40.

The patient was treated conservatively and serially monitored for the haemoglobin level. The lowest level was 5.1 g/dl which was found seven days after admission. There was no evidence of haemodynamic compromise and blood transfusion was thus withheld. She was supplemented with folate 5 mg daily. Her haemoglobin started to rise ten days after admission and was 9.1 g/dl four days later. On follow up a month later, the girl was asymptomatic with a haemoglobin level of 12.6 g/dl.

Discussion

PCH was first described in 1904 by Donath & Landsteiner.[1] In the early 1900's, 90% of the cases were secondary to syphilis, particularly congenital syphilis.[2] The course tended to be chronic relapsing in nature, with haemolytic episode being precipitated by cold exposure, resolving on exposure to warmth. With the fall in incidence of syphilis this chronic relapsing form is now rare.[2] Nowadays PCH is more commonly described as a self-limiting disease predominantly affecting children and may follow infections disease such as upper respiratory tract infection, measles, mumps, chicken pox and influenza.[3-6] The incidence under 10 years of age was estimated to be 0.001/100 000 per year in boys and 0.0005/100 000 per year in girls.[7] The mean age of onset was estimated to be 3.8 years.[7] In a more recent review of 52 patients over a 37-year period the median age of presentation was 5 years and the peak incidence occurred in the group aged 4 years and below.[8] The onset of haemolysis is usually acute and there is often a history of an antecedent viral infection with upper respiratory tract infection being the most common.[7,9] The child may present with leg and back pain, abdominal pain, nausea, vomiting, diarrhoea and passage of dark brown urine.[10] Very often haemolysis occurs without antecedent cold exposure, which was also the case with our patient who presented in the summertime. Haemoglobinuria is often mistaken for haematuria which is far more common.[6] The diagnosis may not be suspected until there is a significant drop in the haemoglobin level which may be of sufficient severity to warrant blood transfusion.

Acute haemolysis in childhood is seldom seen in Hong Kong nowadays after the introduction of population G6PD screening at birth. Haemoglobin H disease is another cause of acute haemolysis in our locality. The diagnosis of G6PD deficiency and haemoglobin H disease can be excluded by G6PD assay and haemoglobin electrophoresis, respectively. Cold agglutinin antibody causing haemolysis is occasionally seen after infection, especially mycoplasma infection. However, severe intravascular haemolysis with gross haemoglobinuria is uncommon. The diagnosis was also excluded by the absence of cold agglutinin. Autoimmune disease such as systemic lupus erythematosis may also cause haemolysis but it is extremely uncommon in this young age.

The exact mechanism whereby different infectious agents induce the immune system to produce Donath-Landsteiner antibodies remains unknown. The Donath-Landsteiner antibody is a biphasic autoantibody. The antibody and complement C1 fix on the red cell in the cold temperature and the subsequent activation of other complement components at a higher temperature causes cell lysis. This cold reactive autoantibody is a complement-fixing IgG with specificity for the P antigen on the red blood cell membrane. This forms the basis of the classic Donath-Landsteiner test.[2] In this test, first the patient's blood sample

is put in ice for one hour, then it is warmed at 37°C for 20 minutes. Another blood sample is incubated at 37°C for 1.5 hours. When both samples are centifuged at 37°C, the supernatant serum will show cell lysis in a positive test. Serological diagnosis in PCH is difficult to make as the Donath-Landsteiner antibodies appear only transiently in the patient's serum. The sensitivity of the test may be improved in the indirect Donath-Landsteiner test when the patient's serum is incubated with donor's group O, P-positive red cells in the presence of added complement (as autologous serum is often complement depleted as a consequence of in vivo haemolysis).[6]

The acute non-relapsing type of PCH seen in childhood, occurring after an acute viral infection, is a self-limiting condition which carries a favourable prognosis even without treatment. The fall in the haemoglobin is dramatically rapid resulting in severe anaemia. Symptoms usually resolve within a month after onset.[8] To date the recommendations for treatment of PCH are based on case reports and case series only. The modalities include blood transfusion and the use of steroid. No randomized controlled trials have been performed to assess the efficacy of either treatment. Generally, blood transfusion is indicated in severe anaemia especially in the presence of cardiopulomary compromise. It is recommended that the donor blood should be warmed before transfusion. The use of P-negative red blood cells is not absolutely necessary, unless haemolysis persists. Keeping the patient warm has been shown to be beneficial. Treating the underlying causes and folate herapy is recommended. There is no evidence suggesting that steroid therapy is beneficial.[2,7] We suspect this case of childhood PCH to be RSV infection related. Whether the use traditional Chinese herbal medicines had contributed to the condition remains unknown. Our patient had a history of repeated intake of herbs since early childhood and yet this was the only episode of haemolysis. In summary, PCH is a rare type of acute haemolysis that is self-limiting but yet potentially serious although our patient recovered uneventfully from this episode of severe haemolysis without treatment. This case report serves as a reminder to paediatricians of its possible occurrence.

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