Paroxysmal Cold Haemoglobinuria and Measles

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With the increasing control of congenital syphilis, paroxysmal cold haemoglobinuria has become a very rare disorder in childhood. Cases which occur now are more likely to be associated with acute infectious diseases (Kissmeyer-Nielsen and Schleisner, 1963). However, despite the frequency of measles in children, paroxysmal cold haemoglobinuria (PCH) has only previously been described as a complication on one occasion (Dacie, 1954). The purpose of this report is to describe a second case of PCH complicating measles and to make some observations on the Donath-Landsteiner red cell auto-antibody involved.

Case Report

Our patient was a 4-year-old girl. Her parents were unrelated and well and she had two healthy sibs. There was no family history of haematological or venereal disease. Immunization (oral polio vaccine, triple antigen, and smallpox vaccination) had been carried out with no ill effects and she had previously suffered attacks of mumps and varicella without complications.

Seven days before the patient's admission on January 31, 1965, her sister developed a typical measles rash and she herself developed a sore throat, cough, and fever. These symptoms continued despite treatment with aspirin, penicillin, and tetracycline. On the day before admission, when her temperature was 41° C. (106° F.), she vomited, had a rigor, and complained of backache. She was admitted to The Hospital for Sick Children, her temperature was 38.3° C. and she looked pale and ill. She was vomiting and had an irritating cough. There was mild conjunctival injection, reddened fauces, and enlarged cervical lymph nodes, but no skin rash. The chest was clinically clear and the cardiovascular system was normal except for a moderate tachycardia. The liver and spleen were not palpable, but there was some tenderness in the loins.

The Hb level on the morning after admission was 8.2 g./100 ml. and the blood film showed occasional spherocytes, normoblasts, and some erythrophagocytosis. There were 7000 WBC/c.mm. (neutrophils 81%, lymphocytes 14%, and monocytes 5%) and 200,000 platelets/c.mm. The serum was the colour of 'strong tea' and gave a strongly positive Schum's test for methaemalbumin. The direct antiglobulin test demonstrated the presence of a non-γ-globulin coating of the red cells, the cold agglutinin titre (4° C.) was 1:8 and the blood group was O, Rh, P1 positive. The urine was dark brown in colour, and contained over 1000 mg. protein/100 ml., and numerous granular casts but no red cells. Methaemoglobin was demonstrated spectroscopically. The blood urea was 45 mg./100 ml., the Paul Bunnell reaction was negative, and the chest x-ray film was clear. The Wassermann, VDRL, and Reiter protein tests were all negative.

The same afternoon a typical measles rash began to develop. The next day the Hb level fell to 4.8 g./100 ml., reticulocytes were less than 1% and spherocytosis and erythrophagocytosis were again noted. The direct non-γ-globulin antiglobulin test remained strongly positive. The direct Donath-Landsteiner test was also strongly positive (Fig.).

She was transfused with whole blood on two occasions during the next 2 days. No difficulty was experienced in crossmatching this blood, either at 37° C. or 20° C. Both transfusions were given slowly and, though she continued to pass dark urine, there was no adverse reaction.

The measles rash faded in 4 days and the haemoglobinuria became less marked. No further fall in Hb occurred, though the direct antiglobulin and direct Donath-Landsteiner tests remained strongly positive for at least another 10 days. During the period of haemoglobinuria, which lasted 11 days, she passed normal volumes of urine and the blood urea did not rise above 53 mg./100 ml.

Hb level 10 days after she was admitted was 9.6 g./100 ml., with 17% reticulocytes, and there was a very occasional spherocyte still present in the peripheral blood film, but no erythrophagocytosis. The diagnosis of measles was confirmed by a rise in antibody titre of from less than 1:4 on the first day of the rash to 1:320 (haemagglutination inhibition test). She was discharged 2 days later (February 12), and her parents were instructed to keep her warm.

Four days later, though the direct Donath-Landsteiner and antiglobulin tests were still positive, there had been...
no recurrence of haemoglobinuria and the haemoglobin was 11.9 g./100 ml.

On March 8 (38 days after the onset of her illness) the patient had been suffering for a week with swelling around the eyes in the morning and a fluctuating red urticarial rash. It was most marked around the neck, behind the ears, and on the chest, arms, and buttocks. It was said to be accentuated by pressure and there was marked dermographia. These manifestations subsided within 2 weeks. The Donath-Landsteiner and antiglobulin tests were negative for the first time since the beginning of her illness. The haemoglobin was 12.7 g./100 ml and the peripheral blood film was normal. Red blood cell glucose-6-phosphate dehydrogenase estimation, haemoglobin electrophoresis, Ham's acid serum test and Crosby's thrombin test for paroxysmal nocturnal haemoglobinuria, and the neutrophil alkaline phosphatase estimation were carried out on this occasion, and all were normal.

Five months after this illness she was asymptomatic. The haemoglobin and peripheral blood film were normal. Repeat Wassermann, antiglobulin, and Donath-Landsteiner tests were all negative (Fig.). The blood urea was 20 mg./100 ml and she passed a normal-coloured specimen of urine with a specific gravity of 1020.

**The Donath-Landsteiner Antibody**

Paroxysmal cold haemoglobinuria is characterized by the presence of the Donath-Landsteiner auto-antibody which has the unique property of sensitizing the red cells during exposure to cold and then causing their haemolysis on rewarming (Donath and Landsteiner, 1904).

Recent work has indicated that, rather than acting as a pan-haemolysin, this antibody has specificity within the P blood group system (Levine, Celano, and Falkowski, 1963; Worledge and Rouso, 1965). In our case this was also true, since serum separated strictly at 37° C. at the height of the patient's illness reacted with all the red cells of a very large panel except for two samples which were of the very rare P^k_ and pp types. The serum reacted with all P_1 and P_2 cells tested, and the patient's own pre-transfusion blood type was known to be P_1.

The direct antiglobulin test, using a Coombs reagent titred to detect both γ and non-γ-globulin (Baxter-Hyland Laboratories), was always strongly positive during our patient's illness. Maximum reactions were obtained with strong concentrations of this antiglobulin serum (no prozone) and the strength of the reaction appeared to be unaffected by absorption with pure γ-globulin. There is still some question as to whether complement is always necessary during the cold phase when the Donath-Landsteiner antibody is actually binding to the red cell (Dacie, 1954; Hinz, 1963), but it seems to be always necessary during the warm phase in order for haemolysis to occur (Dacie, 1954). The positive antiglobulin test in these cases of paroxysmal cold haemoglobinuria is probably due to absorption by the antibody-coated red cells of subhaemolytic amounts of complement.

The actual Donath-Landsteiner auto-antibody in our case appeared to be an IgG globulin, since when
P₁ red cells were incubated at 0° C. with the patient's aged serum, a positive reaction was obtained using the specific anti-γ-globulin Coombs reagent. This reaction was inhibited by prior absorption of the reagent with pure IgG obtained from an ion exchange column. In this respect also, the present case resembles other cases of paroxysmal cold haemoglobinuria recently reported (Hinz, 1963; Worlledge and Roussu, 1965).

Discussion

Thrombocytopenia, most probably due to increased destruction of platelets, is not an uncommon sequel to measles in childhood, but anaemia and haemoglobinuria due to increased destruction of red cells is a rare complication. We have been able to find only one other well-recorded case (Dacie, 1954). In a series of 53,000 cases of measles no such complication was reported (Miller, 1964). In the present case, as in the case previously described by Dacie, the causative agent was demonstrated to be the Donath-Landsteiner red cell auto-antibody.

Paroxysmal cold haemoglobinuria (PCH) is characterized by the passage of haemoglobin in solution in the urine following exposure to cold, together with demonstration of the Donath-Landsteiner antibody in the serum. In the past, congenital syphilis was the commonest cause of PCH, but since the introduction of penicillin an increasing proportion of cases have been described which are unassociated with that disease (Kissmeyer-Nielsen and Schleisner, 1963). Colley (1964) described a case of PCH complicating mumps.

There seems little likelihood of a syphilitic aetiology in the present case, since, as well as the presence of a typical measles rash and a sib with measles, the patient had none of the stigmata of congenital syphilis and her Wassermann reaction was negative on each of the four occasions it was tested, the VDRL and Reiter protein tests being also negative. The Wassermann reactions of both parents were negative. In addition to this, there was a diagnostic rise in the titre of measles antibody.

Case 18 of Dacie's (1954) series was a 3-year-old girl who developed PCH as a complication of measles. Haemoglobinuria began 9 days after the appearance of the measles rash and was only intermittently present for 3 days, whereas in the present case it commenced one day before the rash and was continuously present for 11 days. The Donath-Landsteiner antibody disappeared fairly rapidly from the serum thereafter in both these cases and this appears to be a feature of many of these non-syphilitic cases.

The Donath-Landsteiner red cell auto-antibody was previously described as a pan-haemolysin, but recent work has demonstrated an anti-P₁ + P₂ specificity. However, it is highly unlikely that any of these cases of paroxysmal cold haemoglobinuria can ever be treated by transfusion with 'compatible' red cells of groups Pk or pp, because of the great rarity of these cells (Race and Sanger, 1962).

The most obvious form of treatment of PCH (in addition to treating the underlying disorder) is the avoidance of cold, for if the blood temperature can be kept above the level at which the Donath-Landsteiner antibody sensitizes the red blood cells then its presence will not automatically lead to haemolysis. In the present case haemoglobinuria continued for 11 days, though the patient was always kept warm, and this suggests that at this time the temperature at which the antibody was becoming absorbed onto the red cells must have been fairly high—possibly in the region of 30° C., a temperature that could have been easily reached in the peripheral capillaries. The relatively high temperature at which the antibody may be active appears to be another feature of many of the acute non-syphilitic cases of PCH.

Summary

A case of acute paroxysmal cold haemoglobinuria associated with measles is described in a 4-year-old girl.

Gross haemoglobinuria began 24 hours before the measles rash appeared and lasted 11 days, with no obvious deterioration in renal function. No specific therapy was instituted except for blood transfusion and avoidance of cold. 37 days after the beginning of the illness the Donath-Landsteiner antibody could no longer be demonstrated.

The Donath-Landsteiner red cell auto-antibody involved appeared to be an IgG globulin having specificity within the P blood group system (anti-P₁ and P₂). The positive direct antiglobulin test obtained was due to subhaemolytic amounts of complement absorbed by the sensitized red cells.

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References

The following articles will appear in future issues of this journal:

The 'Happy Puppet' Syndrome. By B. D. Bower and P. M. Jeavons.


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