Paroxysmal Cold Haemoglobinuria

A Case Report

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SUMMARY

The clinical and biochemical findings in a 35-year-old Black man with paroxysmal cold haemoglobinuria are presented. Particular attention is drawn to the possible triggers of the haemolytic process, and the treatment is briefly reviewed.


Paroxysmal cold haemoglobinuria is a rare but interesting condition, in which auto-immune haemolysis may result in massive haemoglobinuria. Most of the cases published so far were related to syphilis.

In view of the rarity of this condition, the clinical and biochemical findings in a patient with probable paroxysmal cold haemoglobinuria are presented.

CASE REPORT

A 35-year-old Black man was admitted to Edendale Hospital on 22 June 1978 with a 4-day history of periodic episodes of abdominal cramps, muscle ache, weakness, and the passage of red urine. These episodes apparently occurred early in the morning when he was taking a cold bath (no hot water was available).

On examination, the patient was severely anaemic and a Labstix test confirmed the presence of blood in the urine which was clear. There was a soft haemic murmur at the base of the heart, and he was normotensive. Neither the liver or the spleen or significant nodes could be felt. The fundi were normal, and there was evidence of slight jaundice.

Further investigations revealed a haemoglobin level of 5.1 g/dl, a reticulocyte count of 9%, a white cell count of 37 900/L and a platelet count of 685 000/L. A presumptive diagnosis of leukaemia was made and a bone-marrow aspiration was done. The result proved to be consistent with intense stimulation of the bone marrow, indicating the presence of acute haemorrhage (?) renal) or haemolysis as probable causes. However, on two occasions microscopic examination revealed no red blood cells or casts in the urine.

On 24 June 1978, however, the patient went into heart failure, most probably due to the severe anaemia, and was transfused with two units of packed cells. It is also worth while to mention at this point that the Blood Bank had great difficulty in acquiring compatible blood for this patient.

Laboratory Findings

The laboratory findings are shown in Table I. The peripheral blood picture showed anisocytosis, increased polychromasia, a moderate number of normoblasts and a neutrophil leucocytosis. Auto-agglutination was present.

A Schumm's test was done and the urine was tested for haemosiderin. Both tests were found to be positive on several occasions. Haemoglobinuria results in the deposition of haemosiderin in the renal tubules derived from the breakdown of haemoglobin. The haemosiderin may be excreted in the urine, probably as a result of desquamation of tubular cells. Haemoglobinuria could not be proved since a spectrophotometer was not available.

Other special investigations carried out to establish the cause of the haemolysis are shown in Table II.

TABLE I. LABORATORY FINDINGS

<table>
<thead>
<tr>
<th>Transfusion</th>
<th>22 June</th>
<th>25 June</th>
<th>23 June</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>5.1</td>
<td>4.0</td>
<td>7.6</td>
</tr>
<tr>
<td>White cell count (x 10^9/L)</td>
<td>37.9</td>
<td>48.3</td>
<td>55.2</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>9.0</td>
<td>18.0</td>
<td>22.5</td>
</tr>
<tr>
<td>Platelet count (x 10^9/L)</td>
<td>685</td>
<td>521</td>
<td>660</td>
</tr>
</tbody>
</table>

TABLE II. SPECIAL INVESTIGATIONS

- Antinuclear factor: Negative
- LE cells: Negative
- Coombs' test: Negative
- Serum iron (μmol/L): 28 (11 - 31)
- Total bilirubin (μmol/L): 21 (2 - 13)
- Total protein (g/l): 110 (60 - 80)
- Albumin (g/l): 34 (38 - 48)
- Rapid plasma reagin test: >1/32
- Treponema pallidum immobilization test: Strongly positive
- Immuno-electrophoresis (g/l): 45.8 (8 - 18)
- IgG: 11.5 (0.6 - 2.5)
- IgM: 6.6 (0.9 - 4.5)
- Protein electrophoresis (serum): Increased gammaglobulin fraction
- Urea (mmol/L): 14.1
- Cold agglutinins (screening test): Negative (1/4)
- Donath-Landsteiner test: Positive
TABLE III. RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Pre-exposure to cold</th>
<th>1 hour</th>
<th>3 hours</th>
<th>5 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>++++</td>
<td>Trace</td>
<td>Negative</td>
</tr>
<tr>
<td>Plasma Hb</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Schumm's test</td>
<td></td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Haptoglobin (mg/100 ml)</td>
<td>&lt;50</td>
<td>-</td>
<td>-</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Bilirubin (μmol/l) Total</td>
<td>12</td>
<td>23</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conjugated</td>
<td>3</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Haemoglobin (g/dl) White cell count (× 10⁹/l) Coombs' test</td>
<td>10,8</td>
<td>10,4</td>
<td>4,9</td>
<td></td>
</tr>
<tr>
<td>Reticulocytes (%) Haemoglobinuria (macroscopical) Red blood cells (microscopical)</td>
<td>10,1</td>
<td>14,7</td>
<td>10,4</td>
<td></td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Negative</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Urobinin</td>
<td>Negative</td>
<td>Trace</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Haemosiderin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Diagnosis**

A diagnosis of paroxysmal cold haemoglobinuria was thus established on the basis of a strongly positive Donath-Landsteiner test. To confirm the diagnosis, Rosenbach's test was performed. The patient's limbs were placed in iced water for 20 minutes. Urine and blood specimens were taken before exposure to cold, and at 1, 3 and 5 hours after exposure to cold. Although the patient did not have a severe reaction, the results were of diagnostic value (Table III). The patient has been on antisyphilitic treatment for 3 weeks and has suffered no further attacks to date.

**DISCUSSION**

Donath and Landsteiner did extensive work on this disease to show that the serum of patients with paroxysmal cold haemoglobinuria contains a haemolysin which, at low temperatures, is fixed to the red blood cells in the presence of complement and becomes activated at 37°C which subsequently leads to lysis of the sensitized erythrocytes.

There is a definite strong association between paroxysmal cold haemoglobinuria and congenital and acquired syphilis, although other aetiological factors also exist. These include infectious diseases such as mumps, measles, infectious mononucleosis and *Mycoplasma pneumoniae* infections. A chronic idiopathic type has also been described.

The clinical features of paroxysmal cold haemoglobinuria occur after exposure to cold and can last from a few minutes to several hours. A typical attack is characterized by abdominal cramps, weakness and general malaise. The patient experiences fever, chills, and during the attack voids urine which varies in colour from pink to that of deep port wine depending on the haemoglobin concentration and the pH of the urine. Anaemia, jaundice, splenomegaly and urticaria may be present.

During these attacks the patient develops anaemia, reticulocytosis, brief leucopenia, followed by brisk leucocytosis, haemoglobinuria, methaemalbuminaemia, thrombocytosis, an increased serum iron level and hyperbilirubinaemia (unconjugated). The urine contains haemoglobin, often accompanied by haemosiderin granules.

In patients with syphilis, treatment consists of antisyphilitic drugs, the avoidance of even minimal exposure to cold, and transfusion if necessary. The effect of immunosuppressive drugs and splenectomy has not yet been proved to be of great value.¹ ²

**REFERENCES**