HAEMOLYTIC ANAEMIA, THROMBOCYTOPENIA AND URAEMIA IN ECLAMPSIA

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Haemolytic anaemia has long been known as a not infrequent complication of eclampsia.[1] Thrombocytopenia may also be associated with eclampsia,[2, 3] while the simultaneous occurrence of both haematological complications has recently been reported by Pritchard *et al.*[4] As these haematological disturbances may have an important bearing on the pathogenesis and therapy of eclampsia, it is the purpose of this paper to draw attention to their occurrence and management, by presenting 2 cases in African patients in whom eclampsia was associated with acute intravascular haemolysis, thrombocytopenia, and uraemia.

CASE 1

J.N., aged 40 (blood group B, Rh-positive), was admitted to hospital on 14 December 1956 with a history of severe headache and blurring of vision of 2 days' duration. Her last menstrual period was in June 1956 and she had not attended an antenatal clinic. Her only previous pregnancy in 1952 was normal. There was no history of drug ingestion or injections.

She was obese, restless and confused. The temperature was 98°F, the pulse rate was 90 per minute, and there was no evidence of shock. Moderate peri-orbital oedema and mild ankle oedema were present. The blood pressure was 260/180 mm. Hg. A heaving apex beat was felt in the 5th intercostal space ½ inch outside the mid-clavicular line, and the aortic second sound was accentuated. Fundoscopy showed extreme narrowing of the arteries, several segments being completely bloodless; marked thickening of the arterial wall and arterio-venous compression were noted; there were superficial haemorrhages and numerous ill-defined white exudates in the retinae; the optic discs were normal. On abdominal examination a 24-week pregnant, non-tender uterus of normal consistency was palpated. Apart from the mental state, the results of examination of the central nervous

system were negative. Two hours after admission the patient had a generalized convulsion.

Investigations on Admission

The urine was dark red in colour, with a specific gravity of 1020. Massive proteinuria was present and microscopy revealed large numbers of red blood-cells. Methaemoglobin was detected on spectroscopic examination.

The cerebrospinal fluid was at a pressure of 240 mm. of water, but was chemically and microscopically normal.

The haemoglobin (estimated as oxyhaemoglobin with a Klett-Summerson photoelectric colorimeter) was 13·1 g.* per 100 ml., leucocytes 15·0 thousand per c.mm. (neutrophils 79·5%, monocytes 2·5%, lymphocytes 17·0% and myelocytes 1·0%), packed cell volume 35%, mean corpuscular haemoglobin concentration 36%, reticulocytes 5%, and normoblasts 750 per c.mm. On the smears the red cells showed marked anisocytosis, moderate poikilocytosis, and the presence of deformed erythrocytes—spherocytes, 'triangular cells', 'helmet cells', and schistocytes. Platelets were not obviously reduced in numbers, although occasional abnormal forms were noted. Methaemoglobin was not detected. The blood urea was 140 mg. per 100 ml.

Course and Treatment

After sedation with paraldehyde, no further fits occurred. The urinary output for the first 24 hours was 60 ml. Treatment with Bull's regime[6] was instituted (Fig. 1). Between 15 and 22 December she became increasingly confused and lethargic, while

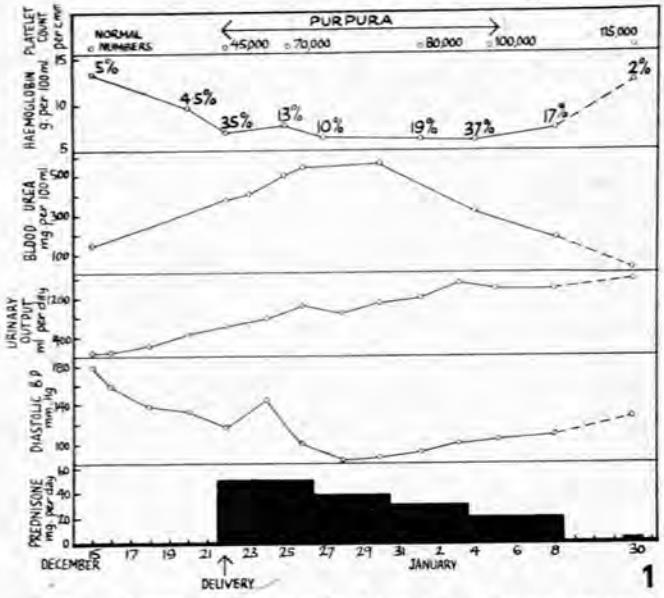

Fig. 1. Course and treatment of case 1. (Percentages on the haemoglobin curve refer to corresponding reticulocyte counts.)

the haemoglobin fell from 13·1 to 7·0 g. per 100 ml. This fall was not associated with overt bleeding or evidence of concealed accidental haemorrhage and was accompanied by marked reticulocytosis (35%), persistent normoblastaemia, a drop in blood pressure to 190/115 mm. Hg, and a rise in blood urea to 383 mg. per 100 ml. On 21 December it was noted that platelets had become scanty on the smears and a wet count showed platelets 45,000 per c.mm. (direct method, using disodium sequestrine as anticoaguiant, and formol citrate as diluent). Schumm's test on that date yielded a positive result. The rapidly progressive azotaemia was associated with an increasing output of dilute urine of specific gravity 1005-1010. On 22 December she was delivered of a fresh, 26-week foetus, with placenta and membranes complete. Blood loss was slight. A few hours later it was noted that there were petechiae over the left side of the chest, the gums were bleeding and there were bruises in the right groin and over the right forearm. Marrow aspirated from the sternum revealed normoblastic hyperplasia (myeloid erythroid ratio 1 : 1·9), with numerous mitotic figures and macronormoblasts. Megakaryocytes were numerous but were not considered to be present in increased numbers; a conspicuous maturation defect was noted, with no cell showing any evidence of platelet budding, and no free-lying platelets were detected. The myeloid series was normal, and no foreign elements were noted in the marrow.

Treatment with prednisone, 12·5 mg. 6-hourly by mouth, was started on 22 December with a view to halting the progressive haemolysis and thrombocytopenia. Over the next 8 days the mental state gradually improved, while the blood pressure after an initial rise, fell to normal levels. The haemoglobin value and platelet count showed little change, reticulocytosis and normoblastaemia persisted, and the bone marrow remained unaltered. Schumm's test on 25 December was again positive. The blood urea continued to rise, reaching its peak on the 8th day, and as before was accompanied by an increasing output of dilute urine. By the 13th day of prednisone therapy the patient was mentally clear, the purpura was resolving, the blood urea was falling rapidly, and the haemoglobin and platelet count were beginning to rise. By the 33rd day of therapy the haematological and biochemical findings were almost normal. The blood pressure, however, had slowly risen and become stabilized around a diastolic pressure of 125 mm. Hg. The urinary output was normal but the specific gravity was fixed at 1010 and the Esbach value was 0·25 g. protein per litre. Fundoscopy revealed that the haemorrhages and exudates had virtually disappeared. The arterial changes remained. Icterus was not observed throughout the entire course of the illness. On 30 January 1957, 40 days after its commencement, prednisone was stopped. The haemoglobin value was now 12·1 g. per 100 ml, reticulocytes 2% and platelets 115,000 per c.mm. The bone marrow had reverted to normal; the myeloid-erythroid ratio was normal, and many platelet-forming megakaryocytes were present.

After recovery from the acute episode the clinical finding of left ventricular hypertrophy was confirmed radiologically and electrographically. Both kidneys showed markedly reduced excretion on the intravenous pyelogram. The phentolamine test was negative.

CASE 2

L.N., aged 38 (blood group A, Rh-positive), was admitted to hospital on 11 January 1957 in a state of stupor. The history (obtained after recovery) was that she had been quite well until the day of admission, when she was suddenly seized with severe headache, vomiting and blurring of vision, followed a few minutes later by loss of consciousness. An accompanying letter from a practitioner who saw her a few hours later stated that a generalized convulsion had been observed. Her last menstrual period was on 15 July 1956 and she had not attended an antenatal clinic. There were 7 previous pregnancies. Of these, 5 were normal, the 4th ended in an abortion at 2 months, while in the last trimester of the 7th pregnancy she was admitted 'with swelling of the feet' to another hospital, where she stayed for 7 weeks before being delivered in January 1954, of a normal infant at the 8th month of pregnancy. There was no history of drug ingestion or injections.

She was moderately obese, restless and stuporose. The temperature was 98·2°F, the pulse rate 96 per minute, and there was no evidence of shock. There was moderate sacral and ankle oedema. Purpuric spots were scattered over the trunk and the proximal parts of the limbs. The blood pressure was 220/140 mm. Hg. A heaving apex beat was felt in the 5th intercostal space, ½ inch outside the mid-clavicular line, and the aortic second sound was markedly accentuated. Fundoscopy showed bilateral papilloedema, numerous white, soft exudates and a few superficial haemorrhages; the arteries were mildly narrowed. Abdominal examination revealed a 26-week pregnant, non-tender uterus of normal consistency.

Investigations on Admission

The urine was dark red in colour, with a specific gravity of 1015. Massive proteinuria was present and microscopy showed large numbers of erythrocytes.

* In Johannesburg (altitude 5,740 feet) the mean haemoglobin value for adult females is 15·3 g. per 100 ml., with lower limit of normal 12·9 g. per 100 ml.[5]

The cerebrospinal fluid was xanthochromic and contained 60 erythrocytes and 1 polymorphonuclear cell per c.mm., protein 90 mg. per 100 ml., and sugar 85 mg. per 100 ml. The pressure was not measured.

Blood count showed haemoglobin 13·8 g. per 100 ml., leucocytes 15·0 thousand per c.mm. (neutrophils 82·0%, monocytes 7·0%, and lymphocytes 11·0%), packed cell volume 38%, mean corpuscular haemoglobin concentration 36%, and reticulocytes 2·5%. On the smears the red cells showed no obvious morphological abnormalities, and no normoblasts were noted; platelets were scanty. The blood urea was 160 mg. per 100 ml.

Course and Treatment

Sedation with paraldehyde was started on admission. The urinary output for the first 24 hours was 400 ml. Treatment with a modification of Bull's regime[6] was instituted (Fig. 2). During the night of 12 January she was delivered of a fresh,

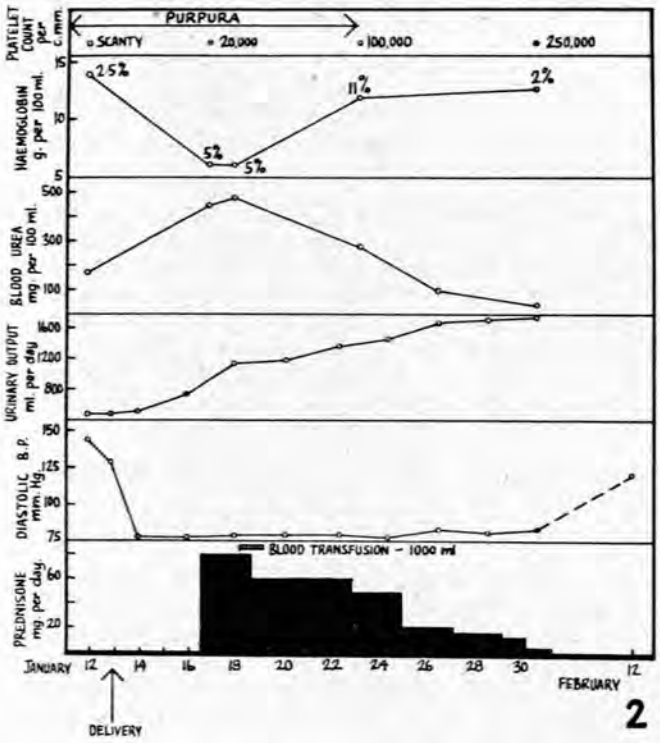

Fig. 2. Course and treatment of case 2.

28-week foetus with placenta and membranes intact. Blood loss was slight. Within 24 hours of delivery the blood pressure fell to normal levels but the stupor continued. On 17 January it was noted that she was pale, despite the absence of an obvious source of bleeding. Blood count now showed haemoglobin 6·4 g. per 100 ml., leucocytes 19·5 thousand per c.mm. (neutrophils 81%), reticulocytes 5%, and normoblasts 975 per c.mm. The red cells showed marked anisopoikilocytosis, with the presence of 'helmet cells', 'triangular cells', schistocytes, and occasional spherocytes. Platelets were 20,000 per c.mm. Schumm's test yielded a positive result. Marrow aspirated from the sternum showed active normoblastic erythropoeisis; megakaryocytes were present in normal numbers, but there was a conspicuous 'maturation arrest' with absence of forms showing platelet-budding, and no free-lying platelets. The myeloid series appeared normal, and no foreign elements were present. The blood urea was 430 mg. per 100 ml., its rise being associated with an increasing output of dilute urine of specific gravity 1004-1010.

In view of the haemolysis and thrombocytopenia, treatment with prednisone, 20 mg. 6-hourly by mouth, was started. On 18 January a transfusion of 1000 ml. of blood was given. Thereafter improvement was so rapid that 14 days after starting prednisone the patient was clinically, haematologically and biochemically normal, apart from the urinary specific gravity, which was fixed at 1010 and the proteinuria of 0·25 g. per litre (Esbach). At no stage of the illness was icterus observed. On 6 February the blood pressure began to rise and eventually became stabilized around a diastolic pressure of 115 mm. Hg.

After recovery from the acute episode an X-ray of the chest confirmed the clinical finding of left ventricular hypertrophy, although the electrocardiogram was normal. The intravenous pyelogram and the phentolamine test were normal.

OTHER LABORATORY INVESTIGATIONS

The results of further investigations carried out on the 2 cases during the phase of acute haemolysis were essentially similar. The serum bilirubin was 0·8, 0·9 and 0·6 mg. per 100 ml. in case 1, and 0·8 mg. per 100 ml. on 2 occasions in case 2. At no stage was urobilin in excess found in the urine. The osmotic fragility of the red cells was moderately increased; case 1 showed 4% haemolysis in 0·55% NaCl, and in case 2 haemolysis commenced in 0·60% NaCl. Heinz bodies were not detected. The direct Coombs test, performed on 4 occasions in case 1 and on 3 occasions in case 2, was negative. Abnormal antibodies could not be demonstrated with enzyme-treated erythrocytes or by the indirect Coombs test. Ham's acid-serum test and the Donath-Landsteiner test were negative, and cold agglutinins were not present. Sickling could not be demonstrated. Paper electrophoresis of haemoglobin in a veronal buffer (pH 8·6) showed a single component with mobility of haemoglobin A. In case 1 alkali resistant haemoglobin was 0·9% and solubility in 2·58 M. phosphate buffer (pH. 6·9, 25°C) 1·30 g. per litre; in case 2 the results were 0·3% and 1·42 g. per litre respectively.

Platelet agglutinins were detected in the sera of both patients; a simple method was used, the platelet suspension being prepared from normal blood, with the use of siliconized apparatus and an anticoagulant comprising equal volumes of 1% disodium sequestrine and 1% 'Triton W.R. 1339'. 0·05 ml. of the platelet suspension was added to 0·05 ml. of the test serum in a siliconed tube and aliowed to stand at room temperature for an hour. The suspensions were then examined microscopically on siliconed slides; in both cases no free-lying platelets remained, while with the control sera the platelets were not agglutinated.

Malaria parasites were not detected, and 'L.E.cells' could not be demonstrated. Section of trephine specimens of bone marrow showed no evidence of hyaline thrombi. Viral and rickettsial complement fixation tests were negative. The V.D.R.L., Kahn, and Kolmer tests were negative; the treponema immobilization test was positive (100% specific immobilization) in case 1 and negative in case 2 (5% specific immobilization). Serum proteins in case 1 were albumin 2·0 g. per 100 ml. and globulin 3·0 g. per 100 ml; in case 2 albumin was 2·9 g. per 100 ml. and globulin 3·7 g. per 100 ml.

DISCUSSION

The essential features of the two cases described above may be summarized as follows:

Both patients had long-standing hypertension as shown by left ventricular enlargement, while case 1 showed signs of well-marked arteriosclerotic retinopathy in addition. This pre-existing hypertension, probably essential in nature, was complicated by eclampsia at the beginning of the third trimester of pregnancy. The eclampsia in turn was complicated by:

(*a*) Acute intravascular haemolysis as shown by rapid fall in haemoglobin (not accounted for by haemorrhage), methaemalbuminaemia (positive Schumm's test), methaemoglobinuria (case 1), spherocytosis and schistocytosis; and compensatory erythropoeisis as manifest by reticulocytosis, normoblastaemia, and erythroid hyperplasia in the marrow (case 1). The increase in the osmotic fragility of the red cells is possibly further evidence of haemolysis, but this finding must be viewed with some reserve, for minor increases in red-cell fragility may occur in normal pregnant women.[7] The absence

of hyperbilirubinaemia and excessive urinary urobilin is consistent with intravascular haemolysis.

(*b*) Thrombocytopenic purpura associated with a megakaryocytic marrow showing defective platelet-genesis, and the presence of platelet agglutinins in the peripheral blood.

(*c*) Acute renal failure.

Treatment of case 1 with prednisone and of case 2 with blood transfusion and prednisone was associated with the resolution of the haematological disturbances and the return of the blood urea to normal levels. Both cases, however, were left with hyposthenuria and mild proteinuria.

Three problems merit discussion.

1. *The Relationship between Haemolysis and Uraemia in Eclampsia*

A striking feature of these cases was the occurrence of severe intravascular haemolysis developing *pari passu* with the rapidly progressive azotaemia. How are these phenomena related? Acute renal failure is a well recognized complication of eclampsia and is usually attributed to ischaemic necrosis on the basis of spasm of the interlobular arteries.[8] Recently evidence has accumulated that azotaemia, irrespective of its etiology, may, when rapidly progressive, give rise to severe haemolytic anaemia. Muirhead *et al.*[9] noted that a progressive anaemia, which was largely haemolytic in nature, occurred in bilaterally nephrectomized dogs, while Chaplin and Mollison[10] found that the survival of transfused, normal erythrocytes was diminished in 6 patients suffering from rapidly progressive uraemia. Swann and Merrill[11] state that severe anaemia is one of the most constant features in the clinical course of acute renal failure, and they suggest haemolysis as a possible mechanism. The pathogenesis of haemolysis in uraemia is unknown. Uraemia, however, cannot explain all cases of haemolytic anaemia in eclampsia, since an analysis of several case reports of haemolytic anaemia associated with severe toxaemia,[4, 12, 13] revealed that haemolysis may be well marked at a time when the blood urea is either normal or only slightly elevated. Nevertheless, even in a patient with pre-existing haemolysis, the supervention of uraemia may significantly aggravate the haemolytic process.

The fact that haemolysis may precede the acute renal failure suggests another pathogenetic sequence. Thus, intravascular haemolysis in eclampsia may cause acute renal failure on the basis of haemoglobinuric nephrosis.[14] The fact that Fahr[15] found haemoglobin casts in the kidney tubules in 18 out of 33 fatal cases of eclampsia suggests that haemoglobinuric nephrosis is a not uncommon complication. The circumstances under which haemoglobinuria produces renal damage are complex. The intravascular injection of considerable amounts of haemoglobin into humans did not produce renal damage.[16] Similarly, haemoglobinuric nephrosis is rare, or has not been observed, in several haemolytic syndromes, such as paroxysmal cold haemoglobinuria, paroxysmal nocturnal haemoglobinuria, and acquired haemolytic anaemia.[17] It is clear that haemoglobinaemia *per se* will not produce haemoglobinuric nephrosis. Yuile[18] showed that the injection of haemoglobin solutions into rabbits did not injure the kidneys. However, when the haemoglobin solutions were injected after the kidneys had been rendered ischaemic by preliminary clamping of the renal arteries for 15-25 minutes, renal lesions closely similar to those of human haemoglobinuric nephrosis were produced. It is possible that the reduction in the renal blood flow in eclampsia may similarly predispose towards the development of haemoglobinuric nephrosis in the presence of intravascular haemolysis. In particular, attention is drawn to the possibility that a degree of interlobular arterial spasm, insufficient by itself to produce acute renal failure on the basis of ischaemic necrosis, may yet do so by predisposing towards haemoglobinuric nephrosis. Fig. 3 shows the possible relationships between haemolytic anaemia and uraemia in eclampsia, and demonstrates how vicious circles may arise.

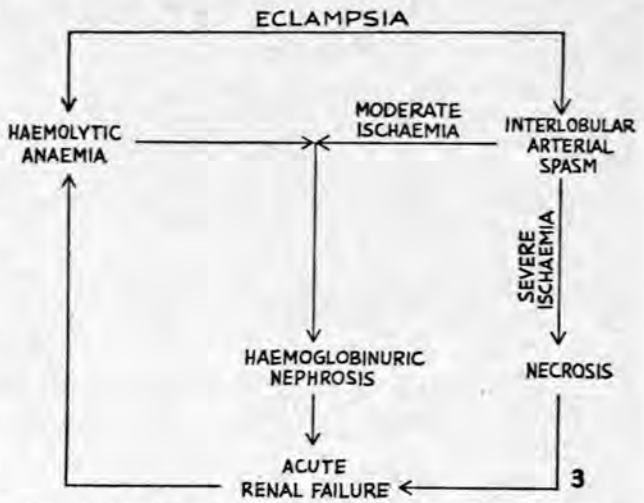

Fig. 3. Possible relationships between haemolytic anaemia and uraemia in eclampsia.

2. *The Relationship between Eclampsia and the Haematological Disturbances*

The possible relationships may be divided into 3 broad categories:

(*a*) The association of eclampsia with the haematological disturbances may be coincidental, the latter being attributable to some other cause. Virtually any type of haemolytic anaemia may manifest itself during pregnancy. However, as has been found by others, it was not possible to demonstrate any of the better-known causes of haemolytic anaemia on clinical or laboratory investigation.

(*b*) The haematological disturbances and the eclampsia may both be due to a common cause. Several workers[19-21] have suggested that eclampsia is best explained as an allergic phenomenon. The fact that pre-eclampsia and eclampsia are strikingly similar to acute glomerulonephritis, a condition generally accepted as allergic in nature, is stressed by Peters.[22] The combination of haemolytic anaemia and thrombocytopenia is not uncommon and points to an immunological disorder. This combination, in the absence of a chemical or infective cause, is generally found in conditions which are thought to be due to an immunological disturbance, such as lupus erythematosus[23] and thrombotic thrombocytopenic purpura.[24] Acquired haemolytic anaemia may be complicated by thrombocytopenia,[25] and the evidence suggests that both the haemolytic anaemia and the thrombocytopenia are due to the formation of auto-antibodies capable of destroying the erythrocytes and the platelets. In the two cases reported above, investigations failed to demonstrate abnormal antibodies against the erythrocytes. This has also been the experience of other workers, with the exception of Pritchard

et al.,[26] who found the direct Coombs test transiently positive in 2 out of 11 toxaemic women. It is of interest that platelet antibodies could be demonstrated in the sera of the two cases reported here; the significance of this finding is however, doubtful, in view of the lack of any agreement on the validity of techniques for the detection of platelet agglutinins. The immunological hypothesis, although suggestive, remains unproved.

(*c*) There remains the possibility that eclampsia in some as yet unknown way may be responsible for the haemolysis and the thrombocytopenia. As pointed out above, the uraemia which may complicate eclampsia is not an adequate explanation for the haemolysis nor, according to Dacie,[27] can it account for the thrombocytopenia.

3. *Therapy*

The possibility that an immunological disturbance underlies the haemolytic anaemia and thrombocytopenia in eclampsia suggested the use of cortisone or one of its related steroids. Certainly the use of prednisone in case 1 and prednisone together with blood transfusion in case 2 was associated with rapid recovery. In particular the prompt rise in the platelet count in case 2 was most gratifying in view of the presence of subarachnoid haemorrhage on admission. Cerebral haemorrhage is a well-known cause of death in eclampsia, and it has been suggested that thrombocytopenia may play an important role in its pathogenesis.[4] Pritchard *et al.*[26] state that the haematological abnormalities undergo spontaneous correction after delivery and it is therefore not possible to attribute the recoveries to prednisone alone. It is clear, however, that prednisone should be given an extended trial to establish its efficacy.

SUMMARY

Two cases of eclampsia in hypertensive African women are described. In both cases the eclampsia was complicated by haemolytic anaemia, thrombocytopenia and uraemia. Recovery was associated with the use of prednisone in one case and the use of prednisone together with blood transfusion in the other.

The pathogenesis of eclampsia and these complications is discussed.

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