Haemolytic-uraemic Syndrome: Survival after Prolonged Oliguria

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Since the original definition of the haemolytic-uraemic syndrome by Gasser *et al.* (1955), there have been many reports of infants and children suffering from this distinctive combination of haematological and renal disorders. The clinical features usually include diarrhoea and vomiting of acute onset, succeeded by pallor and sometimes bruising or petechiae. Oliguria is common but its duration is variable and hypertension occurs in some cases. The blood picture shows a 'micro-angiopathic haemolytic anaemia' (Brain, Dacie, and Hourihane, 1962), with bizarre, distorted, and fragmented red blood cells, burr cells, poikilocytosis, anisocytosis, spherocytosis, and polychromasia. The direct Coombs test is negative, the reticulocyte count is raised, and thrombocytopenia of variable degree is often present. Haemoglobinaemia and haemoglobinuria occur in the more severe cases. The urine contains protein and red blood cells, and the blood urea is raised in proportion to the degree of oliguria. Comprehensive reviews include those of Lieberman *et al.* (1966), Piel and Phibbs (1966), and Habib, Mathieu, and Royer (1967).

The mortality of 150 reported cases was 43% (McLean, Jones, and Sutherland, 1966), death resulting usually from uraemia or its complications. Prolonged anuria or oliguria in this disease is considered of sinister significance, and we, therefore, report here 3 patients with the haemolytic-uraemic syndrome who recovered, with the aid of dialysis, after periods of oliguria of 23, 24, and 15 days duration, respectively.

Case Reports

Case 1. This female infant, born prematurely at 32 weeks (birthweight 1.36 kg.), progressed satisfactorily until June 30, 1963, when at the age of 23 weeks she developed diarrhoea and vomiting. The following day she had

a generalized convulsion and was admitted to hospital where examination showed her to be febrile (38.3° C.), pale, and not dehydrated. Hb was 5.8 g./100 ml., red cells were hypochromic, there was some polychromasia, and platelets appeared normal on the film. She was treated with intravenous fluids, blood transfusion, and sulphonamides; but she continued to pass small watery motions, had a further convulsion, was noted to be anuric, and was transferred to King's College Hospital on July 5. She then weighed 5.5 kg., was oedematous, systolic blood pressure was 60 mm. Hg, the spleen was not palpable, and there was no focal neurological abnormality. Investigations showed Hb 7.1 g./100 ml., packed cell volume 21%, mean corpuscular Hb concentration 30%, the red blood cells showed increased polychromasia and some contracted and burr forms, platelets ample, white blood count 6000 cu.mm., neutrophils 40%. The blood urea was 250 mg./100 ml., sodium 131 mEq/l., and potassium 6.1 mEq/l. Stool culture showed no pathogenic organisms. The blood sulphonamide concentration was 17.5 mg./100 ml., but no sulphonamide crystals were detected in bladder washings.

Complete anuria persisted until July 14, (Fig. 1) and thereafter her urine output remained below 50 ml. daily until July 22, when a slowly increasing diuresis occurred, followed 4 days later by a decline in the blood urea concentration. During this 23-day period of oliguria, 3 haemodialyses were carried out, and after the initial dialysis her blood urea never exceeded 200 mg./100 ml. The only complication of the dialyses was bleeding from the cannula sites, which was controlled by pressure dressings and blood replacement. Subsequent recovery of renal function was slow and at the time of discharge from hospital on October 7, her urine still contained protein and the blood urea was 56 mg./100 ml. Hypertension (200/120 mm. Hg), which had complicated the course of her illness, had remitted by then. An intravenous pyelogram (IVP), cystoscopy, and examination under anaesthetic showed aplasia of the right kidney and a congenital malrotation of the left kidney. The peripheral blood picture showed evidence of continuing haemolysis during the oliguric period, and blood transfusions were given with each dialysis. After the third week of illness a progressive slow rise in haemoglobin concentration occurred, reaching 12 g./100 ml. by the time of discharge.

Received May 22, 1968.

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FIG. 1.—Course of the illness in Case 1.

At the most recent follow-up, 4½ years after the onset of her illness, she weighed 19·8 kg. (50th centile), her height was 97 cm. (10th centile), and BP 110/70 mm. Hg. Investigation showed Hb 13·4 g./100 ml., blood picture normal, blood urea 32 mg./100 ml., plasma creatinine 0·9 mg./100 ml., creatinine clearance 72 ml./min. per 1·73 sq. m., urine protein 35 mg./100 ml., and urine deposit normal.

Case 2. This 17-month-old female infant was admitted to hospital on September 28, 1967, with a history of the passage of frequent, small, loose, yellow stools for 3 days and vomiting for 1 day. She passed no urine during the next 2 days, had a convulsion, and was transferred to King's College Hospital on September 30, 1967. She was then afebrile, pale, and oedematous, had neither purpura nor splenomegaly, and no focal neurological signs. Her blood pressure was 90/60 mm. Hg and her weight 9·8 kg. Investigations showed Hb 5·5 g./100 ml., PCV 17%, MCHC 35%, reticulocytes 5·6%, WBC 11,400/cu.mm., with 47% neutrophils, platelets 65,000/cu.mm. The blood film showed fragmentation and spherocytosis of about 10% of the red blood cells. The plasma contained free haemoglobin, and the direct Coombs test was negative. Urine (October 2) contained haemoglobin, red blood cells, white blood cells, and had a protein concentration of 440 mg./100 ml. and a urea concentration of 580 mg./100 ml. Blood urea 400 mg./100 ml., sodium 126, potassium 5·3, bicarbonate 9 mEq/l., and serum bilirubin 1·8 mg./100 ml., with a negative direct Van den Berg reaction. Stool culture was negative for pathogens.

The progress of her illness is summarized in Fig. 2. Anuria lasted for 2 further days and was succeeded

by a prolonged period of oliguria, the urine output exceeding 200 ml. per day for the first time on October 19. During this 24-day period of oliguria the uraemia was controlled with peritoneal dialysis for 6 hours daily for 17 days. The dialysis was complicated by an episode of bleeding from the catheter site associated with excessive heparin dosage, and by a puncture of the bladder which healed spontaneously. Blood transfusions were given and heparin was administered intravenously in a dose of between 5000 and 10,000 units daily, by two-hourly intravenous injection, from October 5 for 9 days. A rise in the platelet count from 69,000 to 181,000/cu.mm. occurred within 24 hours of starting heparin. The signs of haemolysis regressed and an improvement in red cell morphology occurred more gradually. By October 12 only about 3% of the red blood cells were fragmented. During the course of her illness the spleen became palpable. Because of persisting oliguria, ACTH 15 units intramuscularly daily was started on October 18, and the following day a rapidly increasing diuresis started. The serum concentration of fibrinogen breakdown products (FBP), determined by the tanned red cell haemagglutination inhibition assay technique (Merskey, Kleiner, and Johnson, 1966), remained raised throughout the acute phase of the illness, and showed no evidence of response to heparin.

By the time of discharge from hospital on October 27, Hb was 9·9 g./100 ml., there were only occasional fragmented red cells in the blood film, the platelet count was 379,000/cu.mm., the blood urea 26 mg./100 ml., and plasma creatinine 1 mg./100 ml. The urine, however, still contained red blood cells and protein (257 mg./100 ml.). Her intravenous pyelogram was normal.

FIG. 2.—Course of the illness in Case 2.

At follow-up, 20 weeks after the start of her illness, the spleen was no longer palpable, her blood pressure was 128/74 mm. Hg, Hb 12.7 g./100 ml., with normal red cell morphology, platelet count 150,000/cu.mm., blood urea 29 mg./100 ml., and blood creatinine 0.5 mg./100 ml. The creatinine clearance was 67 ml./min. per 1.73 sq.m., the urine protein excretion was 400 mg./24 hr., and the urine deposit was normal.

Case 3. This girl, aged 3 years 8 months, complained of abdominal pain on October 27, 1967, and the following day developed diarrhoea with 5-6 watery stools daily. Subsequently vomiting occurred, and she was admitted to hospital on November 2, 1967, at which time she had passed no urine for 24 hours. She was anaemic (Hb 6.5 g./100 ml.), dehydrated, and had a palpable

spleen. She was given intravenous fluids and blood transfusion, was found to be oliguric (urine output 30 ml. per day), and on November 4 she was transferred to King's College Hospital. She was then pale, puffy, and afebrile, and weighed 15.7 kg. There was no purpura, blood pressure was 110/75 mm. Hg, and the spleen was enlarged to 2 cm. below the costal margin. Investigation showed Hb 11.6 g./100 ml., reticulocytes 8%, platelets 55,000/cu.mm., white blood count 13,400 cu.mm., with 76% neutrophils. The blood film showed marked fragmentation and polychromasia of the red cells. There was no free plasma haemoglobin. Her blood urea was 410 mg./100 ml., sodium 127, potassium 4.2, bicarbonate 11 mEq/l. The urine protein concentration was 488 mg./100 ml., the urea concentration 840 mg./100 ml., and the urine deposit contained

moderate numbers of red blood cells and white blood cells. Stool culture was negative for pathogens. Culture of a throat swab grew β -haemolytic streptococci and the antistreptolysin-0 titre was 75 units on November 10, rising to over 400 units 7 days later.

Her urine output remained below 50 ml. daily until November 7, and thereafter progressively rose, exceeding 300 ml. a day on November 11, 15 days after the onset of her illness. During this time she was treated with peritoneal dialysis for 8 hours daily for 7 days, with effective control of the blood chemistry. Troublesome bleeding from the peritoneal catheter site occurred on 2 occasions. Blood transfusion was given, and heparin 10,000 to 12,000 units daily was given by continuous intravenous injection from November 5 to November 12. The platelet count remained below 50,000/cu.mm. until November 9, when a slow progressive increase occurred, reaching 140,000/cu.mm. on November 13. The red cell morphology improved progressively, and on November 16, only about 2% of the red blood cells were abnormal. The serum concentration of fibrinogen breakdown products never exceeded 24 μ g./ml. On discharge from hospital on November 24 investigations showed Hb 10.9 g./100 ml., reticulocytes 2%, platelets 216,000/cu.mm., and the blood film showed a few fragmented red cells. The urine protein excretion was 760 mg./24 hr., blood urea 63 mg./100 ml., plasma creatinine 1.1 mg./100 ml., and the IVP was normal.

At follow-up, 19 weeks after the start of her illness, she was clinically well, her blood pressure was 90/70 mm. Hg, and the spleen was no longer palpable. Hb 12.0 g./100 ml., blood film normal, and platelet count 201,000/cu.mm. The urine was free of protein, the blood urea was 29 mg./100 ml., and the plasma creatinine 0.7 mg./100 ml.

Techniques of Dialysis

The haemodialyses (Case 1) were carried out using one coil of the Kolff Twin-Coil artificial kidney, and with the patient on continuously recording weighing scales, by our previously described technique (Anderson, Lee, and Stroud, 1965; Lee and Sharpstone, 1966). The inferior vena cava was cannulated via both long saphenous veins at the groin and the cannulae were kept patent between dialyses by the continuous infusion of heparinized saline solution.

The technique of peritoneal dialysis differed from the standard adult method (Maxwell *et al.*, 1959) in the following respects. A paediatric size catheter ('Trocath', McGaw) was used. The exchange volumes (300 ml. Case 2, and 500 ml. Case 3) were measured by weight change of the dialysate containers which were suspended from a spring balance. To ensure constant temperature of the dialysate this was warmed en route to the patient by passage through a coil of plastic tubing (R66 blood warmer, Baxter Laboratories Ltd) in a thermostatically controlled water bath at 40°C. The patients were weighed two-hourly during the dialyses.

The peritoneal equilibration time was 15 minutes, and this short period coupled with the relatively large sur-

face area of the infant peritoneum resulted in excess removal of water over sodium (Moriarty and Parsons, 1966), with the production of hypernatraemia (plasma sodium 152 mEq/l.) in Case 2. This was corrected by substituting 5% dextrose solution for 50 ml. of each litre of dialysate, reducing the dialysate sodium concentration to 134 mEq/l. Dialysate containing 1.36% dextrose removed 200-400 ml. of fluid each day from the patients and allowed an adequate oral dietary intake and blood transfusion during the periods of oliguria. Hypertonic dialysis, required initially in Case 2 to correct overhydration, was achieved by increasing the dialysate glucose concentration to 2.36% by the addition of 50% dextrose solution. Prophylactic antibiotics were not added to the dialysate which remained sterile throughout. Changing the catheters at the first sign of inflammation around the entry wounds, and in any case after 5 days, perhaps contributed to the absence of peritoneal sepsis.

Discussion

Though at least 40 of the reported patients with the haemolytic-uraemic syndrome have been treated with peritoneal or haemodialysis, there are few reports of recovery after prolonged anuria or oliguria. McQuiggan *et al.* (1965) successfully treated an infant aged 4 months, who was anuric for 17 days, with peritoneal dialysis for 16 days; and also an 11-month-old infant with 2 haemodialyses during a 20-day period of oliguria. Moorhead, Edwards, and Goldsmith (1965) reported a 6-month-old infant who recovered after 14 days of oliguria, during which time 3 haemodialyses were carried out. These cases, together with the 3 patients described here, serve to emphasize that prolonged oliguria does not necessarily indicate irreversible renal damage, and that the current availability of dialysis techniques, which are safe and effective in infants and small children, should reduce further the previously noted decreasing mortality of this disease (Gianantonio *et al.*, 1964).

The renal lesion in the haemolytic-uraemic syndrome is variable, but 4 main histological patterns emerge (Lieberman *et al.*, 1966; Habib *et al.*, 1967)—bilateral cortical necrosis, local or widespread glomerular necrosis, often associated with fibrinoid necrosis of the afferent arterioles, microthrombi in glomerular capillaries, and proliferation of glomerular endothelial and epithelial cells. In other renal disease characterized by glomerular involvement, oliguria of more than a few days duration usually indicates extensive irreversible glomerular damage and a fatal outcome (Merrill, 1957); and indeed in many of the reported fatal cases of the haemolytic-uraemic syndrome, necropsy has revealed lesions such as bilateral cortical necrosis or extensive glomerular necrosis of such

severity that recovery of useful renal function could not have occurred. However, other patients dying of uraemia have had less severe renal lesions at necropsy, and Habib *et al.* (1967) have pointed out the absence of correlation between the initial anuria and the type of renal lesion.

It is possible that suppression of urine in some patients could result from potentially reversible tubular dysfunction rather than from widespread obliteration of glomeruli (Boen, 1965). The haemoglobinaemia and haemoglobinuria, which occur in some cases (e.g. Case 2), could, in itself, be responsible for acute renal failure. Though histologically tubular necrosis is rarely marked in the haemolytic-uraemic syndrome unless glomerular damage is severe (Lieberman *et al.*, 1966), in other varieties of acute oliguric renal failure histological abnormality of the tubules is often insignificant (Brun and Munck, 1957).

In the 14 previously reported patients in whom heparin has been used, an apparently favourable response has been noted in 11 (Hitzig, 1964; Kibel and Barnard, 1964; Künzer and Aalam, 1964; Desmit *et al.*, 1965; Piel and Phibbs, 1966; Dacie, 1967; Habib *et al.*, 1967), the most constant result being a prompt rise in the platelet count. In our Case 2, the platelet count rose from 69,000 to 181,000/cu.mm. within 24 hours of starting heparin, and a decline in the percentage of fragmented cells and of reticulocytes in the blood started at the same time. Despite this improvement, a raised blood concentration of fibrinogen breakdown products was detected throughout the period of therapy. In Case 3 no such dramatic result was observed, though the platelet count rose progressively from 50,000 to 140,000/cu.mm. during the 8 days of treatment. The use of heparin requires careful laboratory control to avoid under- or overdosage. In our patients it was administered by 2-hourly intravenous injection or continuous intravenous infusion and thrombin clotting times were measured daily. The heparin dose was adjusted so that the thrombin clotting time was prolonged to at least twice the control value at 12 seconds, and no greater than 120 seconds. Experience in this laboratory has shown that this range indicates a plasma heparin concentration of between 0.125 and 1.0 mg./100 ml. Despite this control, both patients suffered from bleeding episodes which necessitated the withdrawal of heparin. Our conclusions on the role of heparin in the treatment of the haemolytic-uraemic syndrome must echo those of most previous authors, that though its value is as yet unproven the evidence at present merits its further trial.

The rationale for the use of heparin is based upon evidence that the haemolytic anaemia and thrombocytopenia result from damage to red cells and utilization of platelets by intravascular coagulation. Brain *et al.* (1962) related the micro-angiopathic haemolytic anaemia in a variety of clinical conditions to disease of small vessels rather than to uraemia; and in experimentally induced intravascular thrombosis it has been shown that the degree of haemolysis relates to the extent of the thrombi, and that peak levels of plasma haemoglobin coincide with the release of fibrin breakdown products (Brain and Beck, 1965; Brain and Hourihane, 1967; Brain, Esterly, and Beck, 1967; Regoeczi, Rubenberg, and Brain, 1967). Clinical evidence for the occurrence of disseminated intravascular coagulation is provided by the increased concentration of fibrinogen breakdown products in Case 2, and by the response of the platelet count to heparin.

The administration of ACTH to Case 2 was followed within 24 hours by the onset of diuresis. Most previous authors, however, have found corticosteroids to be without benefit, and we are unable to say whether the result with ACTH in this one patient was anything but coincidental.

Despite intensive investigation of many patients the aetiology of the haemolytic-uraemic syndrome remains obscure. Our Case 3 provided good evidence of an antecedent streptococcal infection, but this association has only rarely been recorded before (Brain, 1963). Other agents such as vaccination (Monnens and Retera, 1965) and virus infection (Gianantonio *et al.*, 1964; Glasgow and Balduzzi, 1965) have occasionally been incriminated, and it seems likely that the aetiology of this condition will prove to be multifactorial.

Summary

Two infants and one child with the haemolytic-uraemic syndrome survived after 23, 24, and 15 days, respectively, of oliguria. Haemodialysis in one patient and peritoneal dialysis in the others effectively and safely controlled the uraemia and allowed adequate blood replacement and dietary intake during the oliguric phase. Heparin treatment was given to 2 patients and was associated with a dramatic increase in the platelet count in one. Good evidence of a preceding β -haemolytic streptococcal infection was obtained in one patient.

We are grateful to Prof. J. Anderson, Dr. C. E. Stroud, Dr. V. Parsons, and Dr. T. P. Mann for permission to report these patients and for their helpful advice.

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