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Case report

Cholestatic jaundice in the haemolytic-uraemic syndrome: a case report

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SUMMARY The haemolytic-uraemic syndrome is the term used to describe the symptom complex of acute oliguric renal failure, haemolysis, and thrombocytopaenia. The pathogenesis of the syndrome is unknown though several factors have been postulated as important. Gastrointestinal disease is now recognised as a regular feature of the syndrome but hepatic involvement is uncommon and limited to occasional jaundice, hepatosplenomegaly and rises in serum transaminase values. A patient is described in whom cholestatic jaundice occurred during the prodromal illness. Its presence is unexplained but might indicate infection with an unrecognised hepatotropic agent or else lack of enteral nutrition during the prodromal phase.

The haemolytic-uraemic syndrome is a disorder, predominantly of young children, in which patients present with acute oliguric renal failure, haemolytic anaemia and thrombocytopaenia.[1 2] In most cases no causative agent is recognised though infection with certain viruses[3] and Gram-negative enteric organisms,[4 5] the taking of oestrogens,[6] pregnancy[7] and the postpartum period[8] have all been associated with the syndrome. The pathogenesis of the condition remains uncertain but recently genetic factors,[9–12] deficiencies of prostacyclin,[10 13 14] antithrombin III or vitamin E,[9 15] the presence of circulating neuraminadase or endotoxin,[16–18] and reduced *in vitro* platelet aggregation[10 13 14] have all been implicated.

The onset of haemolytic-uraemic syndrome is usually preceded by a prodromal illness during which gastrointestinal symptoms, such as diarrhoea with or without bloody stools, vomiting and abdominal pain, commonly occur.[1 19 20] It has been suggested recently that these symptoms may be signs of intestinal involvement in this syndrome and that intestinal disease is a regular feature of this condition.[20] Hepatic complications of the syndrome have also been reported[20 21] but are limited to occasional jaundice, minimal hepatosplenomegaly and rise of serum transaminase values either in the acute phase of the disease or during resolution of the illness. We report a patient in whom cholestatic jaundice was a prominent feature during the prodromal illness of this syndrome.

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Case report

A previously well 13 year old girl developed headache, anorexia, and lower abdominal pain during a family seaside holiday. Her symptoms worsened over the next 12 hours during which time she developed profuse watery diarrhoea. A kaolin mixture was prescribed but was ineffective. Over the next five days the abdominal pain and diarrhoea gradually lessened, but by the sixth day she was noticeably jaundiced. She was admitted to hospital for investigation.

On examination she was dehydrated, pyrexial with a temperature of 37·8°C, and moderately jaundiced; there were no stigmata of chronic liver disease. Small areas of purpura were noted over both upper arms and thighs. The liver was palpable 1 cm below the right costal margin and she was tender over the whole right side of the abdomen but with no guarding or rebound. Sigmoidoscopy to 20 cm showed patchy inflammation and a rectal

biopsy showed a superficial mixed inflammatory exudate which in places involved the surface epithelium.

The haemoglobin was 14·2 g/dl (reference range 11·5–16·0 g/dl), white blood count 20 000×10^9/l with 70% neutrophils (4–11 000×10^9/l), platelet count 66 000×10^{12}/l (150 000–250 000×10^{12}/l, prothrombin time 13 s (control 13 s), blood urea 38 mmol/l (228 mg/100 ml) [3·0–6·5 mmol/l; 18–40 mg/100 ml], serum creatinine 395 μmol/l (4·5 mg/100 ml) [60–120 μmol/l; 0·7–1·4 mg/100 ml], total plasma bilirubin 576 μmol/l (34 mg/100 ml) [5–17 μmol/l; 0·3–1·0 mg/100 ml], conjugated plasma bilirubin 450 μmol/l (26 mg/100 ml) [<3 μmol/l; <0·2 mg/100 ml], serum aspartate transaminase (AST), 184 U/l (5–40 U/l), serum alkaline phosphatase 616 U/l (89 kAu/100 ml) [35–130 U/l; 3–13 kAu/100 ml]. Electrophoresis showed an excess of the liver isoenzyme of alkaline phosphatase.

Over the next 24 hours her condition deteriorated. Her haemoglobin fell to 10 g/dl, her platelet count to 40 000×10^{12}/l and the blood film showed evidence of a gross microangiopathic haemolytic anaemia. The prothrombin time was 13 s (control 12 s), partial thromboplastin time 27 s (control 35 s), thrombin time 23 s (control 16 s), reptilase time 19 s (control 12 s), plasma fibrinogen 3·2 g/dl (32 mg/100 ml) [2·0–4·0 g/dl; 20–40 mg/100 ml], fibrin degradation products 80–160 μg/ml, serum haptoglobins were absent. Despite adequate hydration her urea and creatinine values remained raised and she became oliguric; her urine contained red blood cells in excess of 1000/mm^3 together with occasional red cell and granular casts. A diagnosis of haemolytic-uraemic syndrome was made on the basis of haemolytic anaemia, thrombocytopaenia, and acute oliguric renal failure.

Apart from an insignificant growth of *Escherichia coli* in a urine specimen taken on the third day after admission there was no evidence of recent or of ongoing bacterial infection. In particular there was no evidence of infection with campylobacter, shigella, or salmonella. No viruses were seen on electron microscopic examination, and none isolated in tissue culture from, sputum, nose and throat swabs, urine or stools. Antibodies to hepatitis B surface and core antigens and IgM antibody to hepatitis A virus were negative. Nuclear, mitochondrial and smooth muscle antibodies were absent. Plasma C_3 and C_4 complement, antithrombin III and vitamin E concentrations were normal and there was no evidence of a circulating prostaglandin inhibitor. Ultrasound examination of the liver, biliary tree and pancreas showed no abnormalities.

In the 13 days after admission she received six units of blood, 10 units of platelets, 12 units of fresh frozen plasma and was haemodialysed on three occasions (Fig. 1). She was fed enterally and given folic acid 5 mg daily, but no other medication. Her condition improved with resolution of the jaundice (Fig. 2), microangiopathic haemolytic anaemia and acute renal failure; she was discharged home 31 days after admission. She remains well 15 months after the acute illness with no evidence of residual liver or renal disease.

Discussion

Haemolytic-uraemic syndrome occurs mainly in infants and children[19 20 22] though an increasing number of cases are being reported in adults often in association with ingestion of the oral contraceptive pill and with pregnancy[7 8 23] or as a secondary condition superimposed on essential hypertension.[23] In the United Kingdom 48 cases of haemolytic-uraemic syndrome were reported to the Communicable Disease Surveillance Centre during 1983. The majority occurred during the

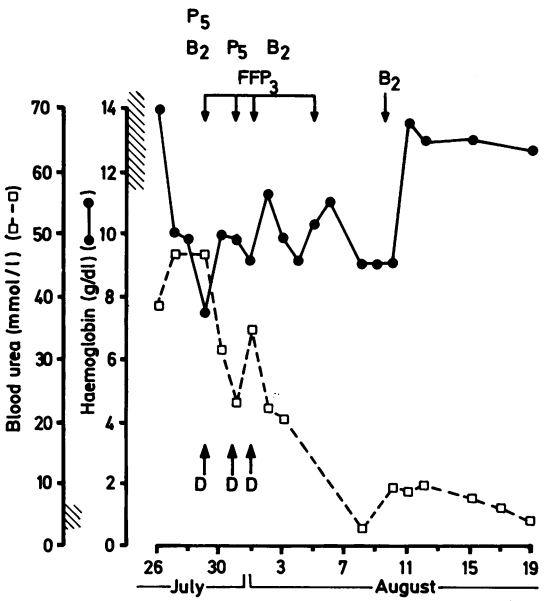

Fig. 1 *Changes occurring in haemoglobin and blood urea concentrations in a patient with haemolytic-uraemic syndrome. D – haemodialysis, P – platelets, B – whole blood, F – fresh frozen plasma. Number of units transfused in subscript. Hatched areas on vertical axes = reference ranges for variables. Urea mmol/l × 6 = mg/100 ml.*

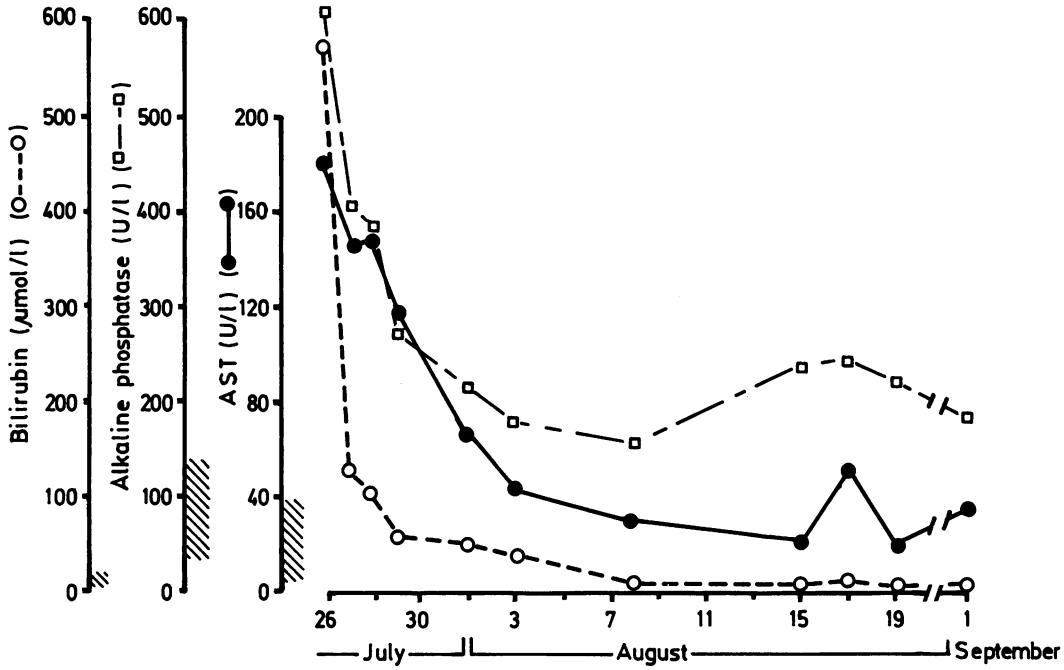

Fig. 2 *Changes occurring in plasma bilirubin, serum aspartate transaminase (AST) and serum alkaline phosphatase concentrations in a patient with haemolytic-uraemic syndrome. Hatched areas on vertical axes = reference ranges for variables. Bilirubin μmol/l × 0·0585 = mg/100 ml, alkaline phosphatase U/l × 0·141 = kAu/100 ml.*

months of July and August and were concentrated in three main epidemics centred on the West Midlands, 20 patients, Sheffield, eight patients and Manchester four patients (Dr M McEvoy, personal communication). The remaining patients, including our own, developed haemolytic-uraemic syndrome sporadically.

The aetiology of the syndrome is unknown though it is likely to be multifactorial. A number of viruses, mainly enteroviruses have been identified during small epidemics of haemolytic-uraemic syndrome either in tissue culture or on the basis of changing serum antibody titres.[3 22 24] There is, nevertheless, no firm evidence linking a specific viral infection with this syndrome. There does, however, appear to be an association between infection with certain Gram-negative enteric organisms such as shigella, salmonella, and *Escherichia coli* and development of this syndrome.[4 5 17 18] Infections with pneumococcus,[25] microtatabiote[26] and yersinia[27] have equally been implicated. In our patient there was no evidence of associated viral or bacterial infection.

In many patients the onset of haemolytic-uraemic syndrome is preceded by an episode of diarrhoea, with or without bloody stools together with abdominal pain and possibly vomiting.[1 19 20] While all patients with haemolytic-uraemic syndrome develop acute haemolysis, renal failure, and thrombocytopaenia it has become increasingly apparent that the disease may also affect other organs. Gastrointestinal symptoms may be prominent and patients may present with a clinical picture similar to ulcerative colitis, appendicitis or intussusception.[9 19 20] Thus the suggestion has been made that the bowel may be involved in a vascular process similar to that in the kidney.[20]

Hepatomegaly, mild icterus and mild to moderate rises of serum transaminase values may occur in the acute stage of the illness but have usually been attributed to the presence of haemolysis. Examination of the livers of patients dying with haemolytic-uraemic syndrome have shown no significant abnormalities.[28 29] In two studies, however, the suggestion has been made that hepatic damage may occur in this syndrome.[20 21] In the first of these the records of 12 consecutive patients with haemolytic-uraemic syndrome were reviewed with respect to gastrointestinal disease. Five patients (42%) had

hepatomegaly while serum transaminase values were raised in all 10 patients in whom they were measured.[20] The authors suggested that these changes might reflect focal hepatic hypoxia, occurring as a result of focal vascular thrombosis, though liver biopsy material was not available for confirmation. In the second study[21] two patients in a series of 31 with haemolytic-uraemic syndrome showed raised serum transaminase and alkaline phosphatase values during the recovery phase that were not associated with a recurrence of the disorder. In one patient jaundice and hepatomegaly also developed. Both patients were given blood transfusions on three occasions during the first week of admission. The subsequent changes in liver function occurred acutely around day 11 in both; a transfusion-related hepatitis cannot therefore be excluded. In our patient there was biochemical evidence of cholestasis coincident with the onset of haemolytic-uraemic syndrome. There was no evidence of biliary obstruction, thus the cholestasis was intrahepatic in origin. While we were able to exclude infections with the common hepatotropic agents it is possible that such an infection may have occurred and might be responsible for the development of the disorder. Alternatively the cholestasis observed in our patient might have resulted from lack of enteral feeding during the prodromal period. Cholestasis has been observed previously in sick children and adults kept fasting and attributed to suppression or lack of hormone stimulation of the hepato-biliary system following withdrawal of oral feeding.[30 31] The prompt reversal of the liver function abnormalities following institution of enteral nutrition in our patient would favour this explanation.

Management of the acute illness involves judicious use of blood transfusion, careful control of fluid and electrolytes and early institution of dialysis. Platelets should be given as indicated. In patients in whom abnormalities of prostaglandin synthesis can be shown, benefit might be derived from use of fresh frozen plasma, the administration of prostacyclin or from plasmaphoresis or plasma exchange. Careful trials are required to assess the value of such treatments.

The prognosis of haemolytic-uraemic syndrome varies considerably from series to series. The outlook is worse in patients who develop the illness sporadically, in those in whom there is no prodromal illness, in women, in older children and adults, in pregnancy and in those in whom the clinical illness progresses rapidly.[9]

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