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CASE REPORTS

Acute reversible renal failure in G–6 PD-deficient siblings

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Summary

Two G–6 PD-deficient siblings, who initially presented with intravascular haemolysis, and later developed acute oliguric renal failure, are described. Renal failure reversed as haemolysis regressed in both patients. The pathogenesis of this complication is reported to be multifactorial but in our patients tubular obstruction by haemoglobin casts is the most probable mechanism. The importance of recognizing this renal complication in G-6 PD-deficient subjects is stressed.

Introduction

Acute renal failure occurring as a complication of drug-induced intravascular haemolysis has been described by various workers (Lindberg and Norden, 1961; MacGibbon *et al.*, 1960). The presence of this complication in glucose 6-phosphate dehydrogenase (G–6 PD) deficient individuals, has been less frequently reported, although a few case reports of reversible renal failure have recently appeared in the literature from this country and elsewhere. Whelton, Donadio and Elisberg (1968) first published a report of two G–6 PD-deficient soldiers suffering from rickettsial disease, who developed acute renal failure following an episode of intravascular haemolysis. A similar complication was later described by Lwanga and Wing (1970), in a 14-year-old African who had G–6 PD-deficiency and recovered completely after peritoneal dialysis. A recent study of six G–6 PD-deficient adult Negroes by Owusu *et al.* (1972) highlighted the importance of associated urinary tract infections in the development of renal failure. Paucity of published data and recent revival of interest in the condition prompted the publication of this report.

Case no. 1

A 16-year-old boy was ill for 6 days with fever which came with chills and rigors and was associated with anorexia and mild cough. Two days before his admission to hospital, the patient developed oliguria and passed highly coloured urine. The patient had taken paracetamol only, before admission. There was no previous histroy of urinary infections, haematuria, jaundice or any similar episode. His temperature ranged from 99 to 102°F (37·2 to 40°C); blood pressure 130/80 mmHg; moderate pallor and mild jaundice without lymphadenopathy; he appeared adequately hydrated. Liver was enlarged 2 cm below the costal margin in the mid-clavicular line, and was non-tender. There was no splenomegaly; kidneys were not palpable; and the renal angles were not tender. Systemic examination revealed no abnormality.

Investigations revealed initial haemoglobin 9 g%; peripheral smear showed normocytic normochromic picture; reticulocyte count was 12%, total leucocyte count 6420/mm^3; polymorphs 60%, lymphocytes 40%; ESR 10 mm (first hour). Urine was dark brown, albumin +++, no bile salts and pigments, no RBC but the haemoglobinuria was confirmed. Red cell fragility to normal saline was impaired; Coombs' test was negative; blood methaemoglobin was positive; serum bilirubin 3 mg%; S.G.O.T. 40 u/ml; S.G.P.T. 54 ml. Glucose-6-phosphate dehydrogenase estimation by using brilliant cresyl blue decolorization test (Motulsky and Campbell Krant, 1961) showed the dye decolorization time to be >180 min, indicating severe G–6 PD-deficiency (normal range 45–60 min). Blood urea was 84 mg percent, serum creatinine 2·2 mg percent, sodium 125 mEq/1, potassium 5·5 mEq/1, chloride 84·6 mEq/1, creatinine clearance rate was 23·5 ml/min.

Progress

Urine output dropped to 300 ml on the second day after admission and within the next 24 hr it was reduced to 150 ml/day. Levels of blood urea rose to 180 mg% and serum creatinine to 4·4 mg%. The patient started vomiting. He was treated with crystalline penicillin, frusemide 80 mg b.d. intravenously, glucose-insulin infusion. Urine output gradually increased within 72 hr to 2100–2600 ml; jaundice and haemoglobinuria also subsided within one week; the renal failure gradually improved and the patient recovered completely.

Case no. 2

A 17-year-old boy (brother of case 1) was admitted to hospital with a history of fever, abdominal pain and vomiting for 4 days; dark coloured urine for one day. He had taken paracetamol for four days and was started on chloromycetin one day before admission. On examination, he looked ill, adequately hydrated, febrile (temperature 40°C) and was moderately jaundiced; pulse was 100/min regular; blood pressure 120/70 mmHg. Systemic examination was normal.

Investigations and progress

Blood—Hb 10·5 g%; peripheral smear—RBC showed moderate anisocytosis and moderate hypochromia and occasional polychromatic cells; there was no malarial parasite; blood methaemoglobin was positive. Dye decolorization time was >120 min. The patient was initially treated with crystalline penicillin and packed-cell transfusions. His temperature was normal after 3 days, but jaundice became deeper. Haemoglobin decreased from 10·5 to 5·4%, reticulocytes were 6·5%. The patient developed oliguria; urine output ranged from 200 to 300 ml/day; blood urea at this stage was 84 mg%, serum creatinine 2·4 mg% and creatinine clearance was 31·5 ml/min. Renal failure was managed with frusemide 100 mg i.v. daily in addition to the other conservative measures. Jaundice subsided on the seventh day and urine output increased to 2220 ml/day. Blood urea and serum creatinine further fell to 36 mg% and 1·3 mg% respectively. The patient was discharged on the twelfth day.

Screening of family members for G–6 PD

None of the other family members reported a history of episodes of intravascular haemolysis. Three brothers of the two patients were tested, G–6 PD-deficiency was demonstrated in only one of them (100 min).

Discussion

Acute intravascular haemolysis following antimalarial therapy with primaquin was, for the first time, associated with G–6 PD-deficiency in the red blood cells by Carson *et al.* (1956). Different races have been reported to have this enzyme deficiency with a variable frequency. A number of structural variants of G–6 PD have been found to mainfest varying severity of haemolysis (McCurdy *et al.*, 1966). A severe grade of deficiency has been reported among Mediterranean subjects. This genetic deficiency has been described from different parts of this country (Baxi *et al.*, 1963; Da Costa *et al.*, 1969; Das, 1972; Jolly *et al.*, 1972).

Exposure to a variety of oxidative agents has been known to induce haemolysis in G–6 PD-deficient subjects. Drugs often incriminated are antimalarials such as primaquin, chloroquin, quinine; analgesics such as aspirin and phenacetin; antibiotics such as

TABLE 1. Summary of clinical and laboratory data of the two patients

Clinical and laboratory data	Case 1	Case 2
Age (years)	16	18
Preceding illness	Fever (6 days)	Fever (4 days)
Drugs taken	Paracetamol	Paracetamol and chloramphenicol
Duration of haemoglobinuria	4 days	3 days
Haemoglobin		
Initial	9 g %	10·5 g%
During admission	3·5 g %	5·4 g %
Blood urea		
Initial	84 mg%	44 mg %
During illness	180 mg %	84 mg %
After recovery	32 mg %	36 mg %
Serum creatinine		
Initial	2·2 mg %	1·8 mg %
During illness	4·4 mg %	2·4 mg %
After recovery	1·6 mg %	1·3 mg %
Liver function test		
Bilirubin	3·0 mg %	5·1 mg %
S.G.O.T.	50 units/ml	50 u/ml
S.G.P.T.	54 units/ml	42 u/ml
Reticulocytes count	12%	6·5%
Coombs' test	negative	negative
Methaemoglobinaemia	present	present
G–6 PD activity (min)	>180	>120
Duration of uraemia	5 days	7 days

chloramphenicol, and others such as nitrofurantoin, PAS, etc. (Motulsky and Stamatoyannopoulos, 1966). The basic mechanism involved in these individuals is the absence of reduced glutathione.

There was a history of brief febrile illness preceding the episodes of oliguria in both patients. Paracetamol and chloramphenicol were administered to them for symptomatic relief. The pyrexia appeared to be of viral origin. It is difficult to incriminate, with any degree of certainty, the drug and/or the viral infection in the causation of renal damage in these cases. Rickettsial infection precipitating haemolysis in G–6 PD-deficient subjects has already been reported by Whelton *et al.* (1968). This, however, seemed unlikely in the two patients, in view of their rapid recovery. While examining post-mortem kidney specimens from 114 cases of fatal rickettsial disease which occurred during World War II, Allen and Spitz (1945) found the fundamental lesion to be an acute diffuse glomerulonephritis with thrombosis of glomerular capillaries and fragmentation of endothelial cells.

The course of events in the two may suggest drug-induced intravascular haemolysis causing acute tubular necrosis. Pathogenesis of acute tubular necrosis occurring in these patients is a matter of speculation. Factors such as shock and dehydration were lacking. Tubular obstruction by the shedded haemogloblin casts is a more plausible explanation of the oliguric renal failure in these patients. This is supported by the fact that renal failure reversed as the haemolytic process regressed on the withdrawal of the possible offending agent. This phenomenon occurring in patients with acute intravascular haemolysis is well documented (Yuille *et al.*, 1947; Goldberg, 1962; Mehta *et al.*, 1971; Owusu *et al.*, 1972). Some of these reports have highlighted the importance of associated anaemia and fulminating urinary tract infections as dominant precipitating factors in the development of this renal complication. These, however, could not be seriously considered as responsible factors in the two brothers. Whether or not renal ischaemia induced by some vaso-constrictor substances released by the lysed red blood cells, as originally postulated by Goldberg (1962), could have contributed, is purely conjectural.

The report indicates that intravascular haemolysis may lead to acute renal failure and all such patients should be screened for G–6 PD-deficiency.

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