HEPATIC COMA AND HEPATO-RENAL SYNDROME DUE TO DRUG HYPERSENSITIVITY

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In clinical practice hepatic coma is not infrequent; usually it is due to hepato-toxic drugs, severe infective hepatitis and portal cirrhosis. Drug allergy giving rise to the same phenomenon is uncommon, though cases of jaundice following PAS therapy have been recorded (Cuthbart, 1950; McKendrick, 1951; Mann, 1953).

The present case merits description because of the rarity and severity of the clinical picture. The patient appeared to recover from this condition, but died from the effects of a neurological lesion which bore no obvious relationship to it.

Case Report

A Jamaican nurse, age 32, was admitted on May 10, 1958, showing in the X-ray left hilar adenopathy and no obvious parenchymal lesion. The condition was later proved to be tuberculous and treatment was commenced with the usual three antitubercular drugs, streptomycin, PAS and isoniazid.

2.6.58. She developed a headache, mild pyrexia and pruritus. Streptomycin was discontinued and symptoms subsided immediately. Her blood pressure was 120/90 mm. Hg.

23.6.58. She developed a sudden, high fever (103°F. to 104°F.) with marked itching and a skin rash. Pruritus subsided as both PAS and isoniazid were withdrawn, though her pyrexia persisted for five days. Urine showed no abnormality and serum bilirubin appeared within normal limits.

3.7.58. A small test dose of PAS (3 g.) caused a transient pruritus and mild erythematous rash.

4.7.58. Intramuscular streptomycin, 0.2 g. as test dose, brought back a high fever (104°F.), pruritus, rash, headache and lachrymation.

5.7.58. She developed a tender hepatic enlargement (about two fingers below costal margin) and was still apyrexial.

7.7.58. The patient had obvious jaundice, but did not appear very ill.

9.7.58. She was noticed to have heavy haematuria and albuminuria, but she remained conscious and coherent.

10.7.58. The patient appeared to lapse into pre-coma and her temperature suddenly became subnormal (96.8°F.). By 4 p.m. she became unconscious. Dietary proteins were withdrawn and a gastric drip was commenced.

11.7.58. She remained in a deep coma with widely dilated pupils. Her temperature still stayed subnormal and the jaundice deepened. No smell of methyl mercaptan was detected. A lumbar puncture was done with negative results. Intramuscular ACTH was given during the day (50 units stat. and 25 units six-hourly). Her blood pressure remained constant at 120/90 mm. Hg.

12.7.58. The condition still deteriorated. A sudden pyramidal type of spasticity appeared in her extremities. ACTH was stopped and a vena caval drip was commenced. Glucose, 400 g., with 400 mg. of hydrocortisone had to be administered intravenously daily. The subnormal temperature soon returned to normal.

Daily biochemical estimations were carried out (Table 1). Liver function tests were estimated regularly during the critical days (Tables 1 and 2) and thereafter. Her blood pressure remained unchanged. Six-hourly catheterization was necessary, as she could not pass urine normally. While she was still comatose a period of oliguria (for about 24 hours only) became evident. The gastric drip had to be continued mainly to give fluids, including fruit juice.

13.7.58. A marked improvement was noticed; coma was lighter and during the evening her corneal reflex returned. Jaundice, however, persisted unchanged and her abdomen slowly got distended. Her blood pressure remained constant. The general condition did not alter significantly during the next 48 hours.

TABLE 1

TABLE 2

TABLE 3

15.7.58. The patient became conscious though confused. She had persistent urinary and faecal incontinence. The oral drip was soon discontinued, as she could retain fluid by mouth. A superimposed urinary infection of *B. coli* was treated with oral chloramphenicol, 500 mg. six-hourly. Parentrovite was also administered intravenously every day.

16.7.58. The patient appeared fully orientated and complained of a pain in her back and some numbness in her feet. A generalized hypotonia was evident at this stage. None of the deep reflexes could be elicited. A bizarre loss of sensation to all forms of stimuli was observed in her lower limbs. The vena caval drip was discontinued.

Hydrocortisone dosage was gradually tapered off within a few days under an 'ACTH umbrella.' Her condition seemed to improve and the jaundice also became lighter. No steroids were administered on July 19 and 20.

21.7.58. Her condition suddenly deteriorated and she lapsed into coma. The abdomen became grossly distended and she developed marked yawning and hiccough. In spite of a high urinary output, her blood urea showed a marked rise (Table 1). The specific gravity of the urine became fixed at 1.010. Prednisone had to be commenced in a high dosage (80 mg. daily) with gantrisin because of another superimposed urinary infection. Within 48 hours her condition improved and her urine became clear.

Mooning of the face was noticed shortly afterwards and the daily amount of prednisone had to be reduced. Following an acute psychotic episode, the steroids had to be withdrawn on July 27. Her blood pressure was elevated to 180/120 mm. Hg., but it returned to the normal level soon.

A chest X-ray following the critical period showed no deterioration. By August 19 she appeared to be improving, though she still had a bizarre sensory loss in her lower extremities.

The subsequent course of this illness was determined by the neurological lesion. Extreme weakness and wasting of the legs developed, with loss of sphincter control. A heavy urinary infection persisted in spite of all efforts to control it, the patient dying of pyelonephritis on September 15.

The post-mortem examination (Dr. Keith Simpson) showed advanced pyelonephritis. Macroscopically the liver was almost normal. There was no evidence of active tuberculosis. The adrenal glands appeared normal. There was a zone of plastic arachnoiditis in the neighbourhood of L1-3. Microscopy showed non-specific chronic inflammatory thickening of the pia-arachnoid. There were few changes in the grey matter.

Investigations

Acid-fast bacilli were isolated by gastric lavage; E.S.R. was 30 mm. one hour (Westergren) on admission. Routine blood and urine examination did not show any abnormality at that period.

For the biochemical changes in blood during the period of crisis, see Tables 1 and 2. Leptospiral agglutination test and Coomb's test were negative. No sickle cells were seen in peripheral blood. At the height of jaundice, red blood cells 4.4 million per cu. mm., platelet count normal, haemoglobin 94 per cent. (Sahli), reticulocyte count less than 1 per cent., and the prothrombin concentration 30 per cent. of normal (prothrombin time 25 seconds and ratio 1:1.6 only). Plasma proteins were always abnormal: one typical picture was a total of 8.6 g. per cent., with albumin 2.25 g. and globulin 6.35 g. (α_1 -globulin 0.4 g., α_2 -globulin 0.45 g., β -globulin 1.3 g., and γ -globulin 4.2 g.). At the height of glycosuria a sample of blood sugar was only 165 mg. per cent. Repeated blood cultures were always sterile.

Lumbar puncture showed clear fluid under normal pressure. The biochemical and cytological findings were normal.

Urinary investigations showed a sterile urine during the earlier period of crisis; later it was infected. Repeated cultures grew *B. coli*. Glycosuria persisted almost all through the critical days (Table 3). Albuminuria, haematuria and urinary casts were also present during these days.

At no time was there any evidence of occult blood in the stool.

Discussion

The occurrence of severe hypersensitivity to anti-tuberculous drugs is not very uncommon. Streptomycin is probably the most frequent cause. Simultaneous sensitization to two or more drugs is not rare (McKendrick, 1951; Houghton, 1954). An altered hyper-susceptible state of the body or some structural similarity between the offending agents may be the cause in such cases (Meyer, 1928).

Common hypersensitivity manifestations include skin rash, at times amounting to exfoliative dermatitis, pyrexia, pruritus, headache, gastro-intestinal disturbances, lymph node enlargement, lachrymation and conjunctivitis, arthralgia and 'pins and needles' in the extremities (Gupta, 1958). Eosinophilia in the blood is not uncommon. Rarer manifestations include albuminuria and haematuria (Nagley and Logg, 1949), encephalopathy (Campanacci, 1949), blood dyscrasia (Sacks *et al.*, 1951), bone marrow aplasia (Womack and Reiner, 1951; Walters, 1953), Loeffler's syndrome (Warring and Howlett, 1952), Wegener's granulomatosis (Wal-

ton, 1958), Fiedler's myocarditis (Chatterjee and Thakre, 1958) and myocardial infarction (Gupta, 1957). Anaphylactic shock as characterized by urticarial rash, hypotension and bronchospasm occurs in about 9 per cent. of the hypersensitive patients (Gupta, 1958), but is probably commoner than penicillin-anaphylaxis (Welch *et al.*, 1953).

Jaundice due to drug allergy needs special emphasis. This is quite a common manifestation of PAS hypersensitivity (Hensler *et al.*, 1957) and many such cases have been reported. Many of them had also developed renal failure (McKendrick, 1951; Livingstone and Street, 1950; Jeffery *et al.*, 1952; Lichtenstein and Canemeyer, 1953; Mann, 1953). Most of these cases, however, were not comatose and the biochemical studies had been scanty. The term 'hepatitis,' as used by these observers to denote the hypersensitivity reactions, is very unfortunate because no inflammation has been observed in the liver biopsies (Sherlock, 1958). Eosinophil infiltration round the portal tracts is common. In some of the patients reported, the level of alkaline phosphatase was elevated and the flocculation tests became positive. These are in marked contrast to the changes observed in the present case. In fact, these features closely simulate a syndrome following methyl testosterone therapy (Kaplan, 1956) or chlorpromazine (Hollister, 1957). The jaundice is an obstructive one and is due to cholestasis (Sherlock, 1958), which, we assume, may arise from intracellular oedema of hepatic cells. The rapid subsidence of the obstructive features with steroids points to a similar conclusion.

Renal manifestations of hypersensitivity reactions are not infrequent (Thomas, 1955). The usual complications are suppression of urine and acute tubular necrosis, haemorrhagic nephritis and an allergic nephritis (Leutscher, 1955; Owen, 1958). Most of the reported cases had renal complications following manifest jaundice, though a reversed sequence was noticed in some patients (Jeffery *et al.*, 1952). Many of the so-called cases of 'nephritis' were true instances of acute tubular necrosis. 'Hepato-renal syndrome' is a special term and it denotes suppression of urine following a period of severe hepatic insufficiency. The pathogenesis is still uncertain (Leutscher, 1955).

In conclusion, we must emphasize the importance of making a correct diagnosis in these cases. Intravenous steroids and noradrenaline may be life-saving (Gupta, 1957; Harvey and Solomon, 1958), if administered in time, before the shock is irreversible.

Summary

A case of simultaneous hypersensitivity to

streptomycin and PAS is described. The patient developed hepatic coma and the hepato-renal syndrome. The biochemical findings during the critical period are presented and discussed. Relevant literature to date is also reported and discussed.

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