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Renal tubular acidosis and cirrhosis

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THE CHARACTERISTIC biochemical disturbance of renal tubular acidosis is a sustained metabolic acidosis with hyperchloraemia, together with an inability to excrete urine of a pH lower than 6.0 in response to an ammonium chloride load (Seldin & Wilson, 1966). In many patients there are also a number of associated abnormalities, such as hypokalaemia, osteomalacia and nephrocalcinosis. Primary forms of the disease are described, and the syndrome can also occur as part of the clinical picture of the Fanconi syndrome. In the latter condition cirrhosis has been described (McCune, Mason & Clarke, 1943; Stowers & Dent, 1947) but we have been unable to find any previous reports of cirrhosis associated with renal tubular acidosis.

Case report

A housewife, born in 1931, had three attacks of pleurisy. The third caused her to be admitted to hospital in 1957, where she was found to have a slightly enlarged liver and a spleen palpable 9 cm below the costal margin. She was not jaundiced, but a few spider naevi were noticed on her hands and wrists. Liver function tests: serum bilirubin, 0.7 mg/100 ml; alkaline phosphatase, 13 K.A. units/100 ml; zinc turbidity, 40 units; thymol turbidity, 12 units; serum albumin, 3.0 g/100 ml; serum globulin, 4.8 g/100 ml; with an electrophoretic strip showing a diffuse increase in γ -globulin. A liver biopsy showed small nodules of apparently normal parenchymal cells, separated by interstitial tissue containing a moderate infiltration of chronic inflammatory cells. Further tests performed at the Hammersmith Hospital (Professor Sheila Sherlock) included a barium meal

which revealed no oesophageal varices, and a splenic venogram which showed a patent portal vein with small collaterals passing to the left gastric and umbilical veins. The intrasplenic pressure was 14 mmHg. Unfortunately no measurement of her plasma electrolytes was made at this time.

Two years later, in 1959, she was admitted to hospital with the signs and symptoms of hypokalaemia. She was drowsy, with pain and weakness in her limbs, and polyuria. Plasma potassium levels on two occasions were 2.7 and 3.2 mEq/l. More detailed investigations showed her to have renal tubular acidosis, with plasma electrolytes of: chloride, 124 mEq/l; bicarbonate, 14 mEq/l; and sodium, 143 mEq/l. Urinary potassium excretion was 72 mEq/24 hr on a day when plasma potassium was 2.8 mEq/l. After receiving 3 g of ammonium chloride daily for 6 days, the minimum urine pH obtained was 6.8. Serum calcium, 9.2 mg/100 ml; urinary calcium excretion, 328 mg/24 hr; creatinine clearance, 108 ml/min. Straight X-ray of the abdomen: renal shadows normal. A catheter specimen of urine contained a trace of protein and only occasional pus cells. However, a renal biopsy (Professor H. E. de Wardener) revealed a chronic patchy inflammatory cell infiltrate, associated with ischaemic changes in the glomeruli, suggestive of pyelonephritis. She was discharged on potassium bicarbonate and citrate supplements, to which were later added rotating antibiotics.

During the next 5 years there was little change in her condition. In April 1966 she stopped taking potassium supplements and was readmitted, semi-conscious and dehydrated, with marked muscular weakness. Plasma electrolyte levels were similar to

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her previous admission: potassium of 2.7; sodium of 140; chloride of 117; bicarbonate of 12 mEq/l; blood urea, 40 mg/100 ml. She was treated over 3 days with intravenous potassium supplements. Subsequently, on an oral intake of 300 mEq potassium per day, measurements of the total exchangeable body sodium and potassium gave values of 51.5 and 44.5 mEq/kg respectively. These are within the normal ranges for women of 40.2 ± 8.3 and 41.2 ± 9.2 mEq/kg, respectively (Flear *et al.*, 1958). A new finding was the presence of bilateral nephrocalcinosis (Fig. 1). The 24-hr urine calcium ex-

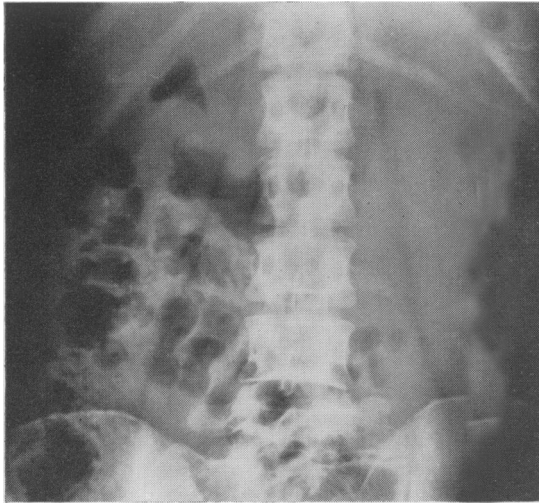


FIG. 1. Straight X-ray of abdomen in 1966 showing bilateral nephrocalcinosis.

cretion on a normal ward diet was 126 mg; the plasma phosphate, 4.9 g/100 ml; and the serum calcium, 8.3 mg/100 ml. A skeletal survey showed no evidence of osteomalacia, and chromatography of the urine revealed a normal pattern of amino-acid excretion. There was no glycosuria. Maximum urine concentration achieved in response to Pitressin (5 Units s.c.) was 1.010.

The clinical signs of the liver disease were unchanged, and there was no evidence of portal systemic encephalopathy. Liver function tests: serum total bilirubin, 1.3 mg/100 ml; serum glutamic oxaloacetic transaminase, 40 S.F. units; serum alkaline phosphatase, 23 K.A. units/100 ml; the serum albumin was 2.5 g/100 ml and the serum globulin was 4.8 mg/100 ml. Electrophoresis again showed a marked increase in γ -globulin. Bromsulphthalein retention at 30 min, after an intravenous dose of 5 mg/kg body weight, was 52%. An electroencephalogram was normal. A liver biopsy showed changes similar to those seen previously, with small nodules, portal tract fibrosis and minimal cellular infiltration. The intrasplenic

pressure was 17 mmHg, and again there were no oesophageal varices on barium swallow examination. The plasma caeruloplasmin was 23 mg/100 ml, and the serum copper 81 μ g/100 ml [normal values for our laboratory 29 (S.D. 5) and 84 (S.D. 13) respectively].

Chest X-ray: accentuation of the pulmonary vascular markings in the lower lung fields, which had not been present in X-rays taken in 1957. Lung function tests: a normal ventilatory capacity with a peak expiratory flow of 300 l/min, FEV₁, 2400 ml. Exercise ventilation was also normal, the resting arterial oxygen saturation being 98.5%, with no change after 5 min exercise.

Family studies

The father died of pneumonia at the age of 57 years. The mother was alive and well at the age of 75. Five of the patient's nine siblings, her two children, and seven children of two of her siblings were examined clinically and had serum electrolyte estimations performed. Clinical examination was negative and although a number had serum potassium values at the lower limits of the normal range, the plasma bicarbonate was normal in all (Fig. 2).

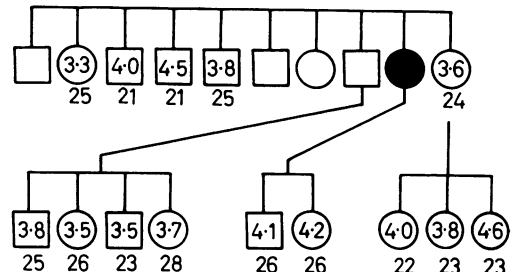


FIG. 2. Results of family investigations. Key: \square and \circ , Not tested; \bullet , proband. Figures within symbols are plasma potassium and below symbols plasma bicarbonate, both in mEq/l.

Plasma chloride values were also normal, falling within the range of 97–105 mEq/l. Abdominal radiographs on one sister who had complained of bilateral loin pain for several years were normal. Liver function tests (including bromsulphthalein retention) done on this sister, and on the patient's eldest daughter aged 12, were also within normal limits.

Discussion

The present patient showed all the biochemical features of pure renal tubular acidosis, and the sex, age of onset and lack of known antecedent causes would also suggest that this was the primary form of the disease. The development of nephrocalcinosis was clearly a secondary feature as shown by the serial radiographs. Nephrocalcinosis is pre-

sent in 73% of cases of renal tubular acidosis (Wrong & Davies, 1959) and is believed to be due to excessive calcium excretion in an alkaline urine that contains too little citrate (Dedmon & Wrong, 1962). There was histological evidence of pyelonephritis early in the course of the disease in the present case, but although Albright & Reifstein (1948) considered pyelonephritis to be a cause of renal tubular acidosis, more recent workers believe that it develops secondarily in a kidney adversely affected by hypokalaemia (Seldin & Wilson, 1966). Although the defect in primary renal tubular acidosis is believed to be genetic in origin investigations of the family, as in the present case, are often negative, and a positive family history was found in only four of the sixty cases reported by Piel (1957).

The relationship of the cirrhosis to the renal lesion is uncertain. Histological abnormalities in the kidney are common in cirrhosis of various types, but the lesions are predominantly glomerular (Patek, Seegal & Bevans, 1951). Renal tubular acidosis has been described in Wilson's disease (Morgan *et al.*, 1962), and in galactosaemia, in which cirrhosis can develop (Huth, Webster & Elkinton, 1960), but both these conditions were excluded. Possibly relevant to the present case, however, is the recent report by Morris, Johnson & Fudenberg (1964) of renal tubular acidosis in association with hyperglobulinaemia. The three female patients described had idiopathic hyperglobulinaemia, lupoid hepatitis and Sjögren's syndrome. Serum globulin levels were 5.6, 5.9 and 7.9 g/100 ml, respectively, and in each case the predominant globulin was a broad base IgG (7S γ -globulin). Moderate hyperglobulinaemia has been a feature of the present patient throughout.

It is to be noted also that liver disease has been described in the Fanconi syndrome, in which renal tubular acidosis may be present as a component of the multifactorial disturbance in renal function. McCune *et al.* (1943) found hepatic changes at autopsy in seven of twelve patients with the Fanconi syndrome. Two had cirrhosis, four focal necroses and one, fatty infiltration. They concluded that the liver disease in four of the cases was due to accompanying cystinosis, for they observed encroachment of masses of cystine crystals on the liver cells, producing necrosis. However, Stowers & Dent (1947), in describing detailed studies in a man with the Fanconi syndrome, but without cystinosis, who at autopsy had cirrhosis and a hepatoma, thought that the cause was possibly methionine and cystine deficiency secondary to the aminoaciduria. The present patient, however, had neither cystinosis nor an abnormal aminoaciduria.

One interesting finding in connection with the cirrhosis was the development of pulmonary changes. The appearances were those of increased vascular markings, with ill-defined mottling, and it is possible that they were due to arteriolar dilatation and lung spider naevi as recently described by Berthelot *et al.* (1966). Although hepatic precoma in patients with cirrhosis may be aggravated by hypokalaemia (Read *et al.*, 1958), the present patient had at no time shown signs of portal systemic encephalopathy. However, more recent work suggests that this aggravation is due to the commonly associated metabolic alkalosis rather than depletion of body potassium (Casey *et al.*, 1965). Alkalosis may render the blood-brain barrier more permeable to the ammonium ion (Warren *et al.*, 1960), and it is possible that our patient is protected by the metabolic acidosis.

Summary

The case history of a female who was found to have cirrhosis at the age of 26 and renal tubular acidosis 2 years later is described. Throughout the 9-year follow-up period, her symptoms have derived from the renal lesion and the cirrhosis has shown little progression. No involvement of the family was found. The relationship of the cirrhosis to the renal tubular acidosis is discussed.

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