Nephrotic syndrome complicated by tubular dysfunction. Case report and review of possible mechanisms

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Summary

A 35-year-old-man presented with nephrotic syndrome due to mesangiocapillary glomerulonephritis; he later developed a potassium-losing state, generalized amino aciduria and glycosuria. Clinical and biochemical improvement occurred after steroid therapy. The possible pathophysiological mechanisms are discussed.

Introduction

Abnormalities of proximal renal tubular function in the nephrotic syndrome are rare but well documented (Bruck, Rapoport and Rubin, 1954; Kovnat and Lin, 1974; Pabico *et al.*, 1976), particularly in children. The mechanisms underlying this combination remain obscure; a number have been proposed (Vitacco *et al.*, 1970) including the recent speculation that a common mechanism linked by immune-mediated processes could be at work in some cases (Shwayder *et al.*, 1976). In addition, little is known about the effect of steroid or other therapy in this mixed syndrome.

A case is now reported of an adult with nephrotic syndrome due to mesangiocapillary glomerulonephritis (MCGN) who subsequently developed a potassium-losing state, generalized amino aciduria and glycosuria. His course and response to steroids are described and the possible mechanisms underlying his disease are considered.

Case report

A 35-year-old butcher presented in August 1976 with a 4-month history of backache and swelling of the ankles, which had gradually progressed to involve the legs, abdomen and face. He had gained weight, and his urine had become frothy in the previous 2 months. He had had a sore throat 4 months previously but never had any skin or joint trouble. In the past he had been asthmatic with allergies to pollen and animal furs, but had

been desensitized in 1971. He had had scarlet fever in his teens and viral meningitis in 1971.

Examination showed gross oedema extending to the umbilicus and involving the face. He was normotensive (BP, 130/80 mmHg), and the kidneys were not palpable.

Initial investigations revealed the following: Plasma urea, 37 mg/100 ml (6.1 mmol/l); plasma creatinine, 1.1 mg/100 ml (98 µmol/l); potassium, 3.4 mmol/l; sodium, 137 mmol/l; chloride, 88 mmol/l; bicarbonate, 23 mmol/l; total serum protein, 49 g/l; albumin, 15 g/l; globulin, 34 g/l; 24-hr urine protein excretion, 10.5 g; urine protein electrophoresis showed albumin, α_2 and β globulin; creatinine clearance, 90 ml/min; 24-hr urine electrolyte excretion normal (potassium, 41 mmol; sodium, 17 mmol; chloride, 34 mmol); no glycosuria; amino acid chromatogram normal; urine microscopy normal; screening culture negative; ANF negative; serum cholesterol, 17.0 mmol/l; liver function tests normal; Hb, 16.3 g/l; WBC $8.2 \times 10^9/l$, neutrophils 80%; lymphocytes 16%; ESR 81 mm in 1st hr. Chest X-ray and IVU normal.

A renal biopsy showed glomeruli with accentuated lobularity, mesangial hypercellularity, and capillary wall thickening. The tubules were mostly normal, although early atrophic changes were present in places (Fig. 1).

A diagnosis was made of nephrotic syndrome due to early MCGN. The subsequent course was marked by heavy proteinuria up to 23 g/24 hr and resistant oedema requiring constant changes in diuretic therapy (Fig. 2). There was a drop in renal function but creatinine clearance was never < 39 ml/min (Fig. 2). During his 30-month course, serial estimations of circulating immune complexes were performed on 22 occasions. Elevated levels were found 5 times; in 3 of these CH_{50} (total haemolytic complement) was reduced. The appearance and disappearance of elevated levels of circulating immune

FIG. 1. First renal biopsy showing early mesangiocapillary glomerulonephritis and only minor tubular degenerative changes (HE, $\times 32$).

FIG. 2. Clinical course and treatment.

complexes bore no relationship to the clinical course and may well have been due to unrelated infections. C₃ levels were always within the normal range, and anti-DNA antibodies were never > 11 u./ml (normal < 24 u./ml).

There was evidence that certain proximal tubular functions became abnormal during his illness (Fig. 3). Urinary potassium excretion increased from 41 mmol/day to 226 mmol/day and the patient required large oral potassium supplements, up to 160 mmol/day. Serum potassium levels were persistently below the normal range after October 1976, reaching a low of 1.8 mmol/l. Potassium levels and supplement requirements bore no relationship to the dose or type of diuretic given (Figs 2 and 3). The amino acid chromatogram became abnormal, showing a generalized amino aciduria, and clearance values of 17 endogenous amino acids were measured, 15 of which were above the normal adult range (Table 1). Glycosuria was first noted in November 1976 and this became a constant feature. Investigation revealed a urinary glucose concentration of 5.6 mmol/l with serum glucose concentration of 3.8 mmol/l. Urinary protein electrophoresis in December 1978 showed a heavy band of β^2 microglobulin in addition to a highly selective glomerular protein pattern (albumin and β globulin only).

TABLE 1. Endogenous renal clearance of amino acids

	Clearance ml/min/1.73 m ² October 1978	March 1979	Normal adult control range
Taurine	6.35	5.12	1.7-14
Aspartic acid	—	0.8	0-2.4
Threonine	8.6	4.16	0.8-1.5
Serine	35.94	8.3	1.9-1.5
Glutamic acid	0.63	0.38	0.3-0.7
Glutamine	11.16	5.97	0.7-1.8
Glycine	11.98	12.13	2.7-5.8
Alanine	4.16	3.0	0.3-0.9
Cystine	5.19	9.6	0.7-2.9
Valine	0.9	0.6	0.1-0.3
Methionine	4.2	0.9	1.1
Isoleucine	1.27	0.51	0.2-1.0
Leucine	1.84	0.8	0.2-0.9
Tyrosine	4.5	4.0	1.0-1.7
Histidine	15.2	5.76	4.7-9.1
Ornithine	3.48	1.76	0.2-0.5
Lysine	4.3	1.16	0.2-1.9
Arginine	1.31	—	0.2-0.8

The poor clinical state of the patient prompted a review of his management and he was re-admitted in November 1978 for a second renal biopsy. This showed an advanced MCGN, with sclerosis of many glomeruli. The tubules in this sample were markedly atrophic, with interstitial fibrosis and

FIG. 3. Some parameters of tubular function and potassium requirements.

lymphocytic infiltration (Fig. 4). By immunofluorescence microscopy, granular deposits of IgG and C₃ were detected in glomerular mesangia and capillary loops; no immunoglobulins or complement components were associated with tubular basement membranes.

It was decided to start a course of prednisolone empirically, and at the time of writing (1979) he had made an excellent response. The oedema disappeared and he required no diuretics by the middle of December 1978. Urine protein excretion fell to 0.35 g/24 hr and serum albumin rose to 42 g/l, while the creatinine clearance returned to normal (117 ml/min).

Further studies of proximal tubular function also indicated considerable improvement. The serum potassium rose to normal (Fig. 3) while potassium requirements dropped to 40 mmol/day. Urine potassium excretion fell to 49 mmol/day, and glycosuria disappeared. The amino acid chromatogram and the repeat amino acid clearance studies (Table 1)

showed a reduction in amino aciduria. In addition, urine acidification and concentration tests were both normal (Table 2), as were 24-hr urinary excretions of phosphate (34 mmol/24 hr).

TABLE 2. Urine acidification and concentration tests

Time (hr)	Urine pH	Urine concentration (mosmol/l)
0	6.3	842
1	6.3	902
2	5.5	920
3	5.5	817
4	5.7	836
5	6.2	868
6	6.3	—

Note: Urinary acidification test performed by giving the patient 0.1 g/kg body weight ammonium chloride orally and measuring urine pH at hourly intervals for 6 hr.

Urinary concentration was measured by giving the patient 0.4 µg of desmopressin i.m. at 8 p.m. and measuring urinary osmolality the following morning for 6 hr. Water was not restricted.

FIG. 4. Second renal biopsy showing advanced tubular atrophy and dilatation, and interstitial fibrosis. The glomerulus at the top of the field is almost completely hyalinized (HE, $\times 42$).

Discussion

This patient presented with the nephrotic syndrome and developed a potassium losing state, glycosuria and amino aciduria. Abnormalities of proximal tubular function in the nephrotic syndrome are not generally seen until end-stage renal failure has been reached (Bruck *et al.*, 1954), but there are well documented cases of proximal tubular abnormalities and nephrotic syndrome in the absence of end-stage uraemia in children (Shwayder *et al.*, 1976; Stanbury and Macaulay, 1957; Burke *et al.*, 1971) and adults (Sherman and Becker, 1971; Weinreb *et al.*, 1970). The pathophysiological mechanisms underlying tubular damage in this context remain unknown, but many have been proposed, including the damaging effect of heavy proteinuria (Pabico *et al.*, 1976; Weinreb *et al.*, 1970), hypokalaemic nephropathy (Stanbury and Macaulay, 1957), glycogen deposition in distal tubule cells (Kovnat and Lin, 1974), specific autoimmune tubular and glomerular disease (Shwayder *et al.*, 1976; Naruse *et al.*, 1976) and the general tissue damage associated with end-stage glomerulonephritis and uraemia (Sherman and Becker, 1971). A variety of histological patterns has been described in this mixed syndrome, the most common of which is MCGN with immune complex deposition (Dreher, Zimmerman and Simpson, 1977; Vitacco *et al.*, 1970). Other patterns reported include 2 cases of focal segmental sclerosis (McVicar, Exeni and Susin, 1974), and one of membranous glomerulonephritis (Kovnat and Lin, 1974). Tubulointerstitial nephritis is seen in most cases but there is probably no relationship between this histological feature and biochemical abnormalities of tubular function (Dreher *et al.*, 1977).

The lack of clinical and pathological uniformity in these patients makes it unlikely that there is a single underlying mechanism causing tubular damage. Most of the childhood cases progressed rapidly to renal failure (McVicar, *et al.*, 1974; Burke *et al.*, 1971) and in these patients it seemed reasonable to explain tubular dysfunction as being secondary to gross renal damage and uraemia. Some authors have considered that this may always be the case; there is indeed a growing body of experimental evidence that in nephrotic syndrome with good renal function, both tubular function (Maddox *et al.*, 1974; Andreucci *et al.*, 1973; Oken and Flamenbaum, 1971) and morphology (Ryabov *et al.*, 1978) are essentially normal and able to compensate appropriately for the changed intraluminal and peritubular environment. Sherman and Becker (1971) showed in 22 adult patients with nephrotic syndrome that glycosuria and lysozymuria were correlated with the degree of renal function rather than urinary or serum protein concentrations. Other authors have, however, emphasized the specific tubular damaging

effect of hyperosmotic albuminuria, particularly when >3.5 g/24 hr (Pabico *et al.*, 1976; Weinreb *et al.*, 1970). In the present case, however, the abnormalities in proximal tubular function correlated with the degree of proteinuria as well as with the level of renal function, both before and after steroid therapy.

Hypokalaemia was a marked feature in the present patient. There is doubt, however, whether hypokalaemic nephropathy can explain the glycosuria, amino aciduria and potassium-losing state. The classic features of hypokalaemic nephropathy do not include a severe potassium-losing state (Hollander and Blythe, 1971), and a renal concentration defect is usually present, which was not so here (Table 2). The expected histological features of collecting duct vacuolation and foamy swelling were also absent.

There may be other possibilities. Prompted by some cases of anti-tubular basement membrane antibody associated with the Fanconi syndrome (Levy, Gagnadoux and Habib, 1974; Bergstein and Litman, 1975), there has been much interest in immune-mediated tubular disease. There have been a number of reports of immune complex-associated MCGN characterized by the presence of a renal tubular epithelial antigen (RTE) in the glomerulus (Naruse *et al.*, 1974; Ozawa *et al.*, 1975; Pardo *et al.*, 1975) and experimental work has confirmed this (Heymann *et al.*, 1959). In all these cases the glomerular disease was unassociated with any tubular abnormality. An exception, however, is a recent report of a 6-year-old girl who developed glycosuria, amino aciduria and phosphaturia together with the nephrotic syndrome (Shwayder *et al.*, 1976). Biopsy showed MCGN with RTE in the glomeruli and positive immunofluorescence for IgG and complement in the glomeruli and tubules. Circulating immune complexes containing RTE were isolated. In the present case circulating immune complexes were not a consistent feature (see above) and although the authors did not stain for RTE, no IgG or complement products were seen in the tubules.

The pathological mechanism in this case remains unclear. The most plausible explanation seems to be the effect of heavy proteinuria, but the effect of general tissue damage or an immune mechanism have not been excluded. The marked response to steroid therapy of both glomerular and tubular function seems to point to a common mechanism.

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