Renal lesions in leprosy amongst north Indian patients

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Summary

Sixty consecutive patients with leprosy were investigated for renal involvement. Clinically overt renal disease was present in 4 patients; 3 presented with a nephrotic state and one patient with progressive renal failure. Urinalysis showed daily protein loss ranging from 0.4 to 8.9 g in 8 patients and microscopic haematuria in 4 cases. Elevated levels of blood urea and creatinine were seen only in one patient with diffuse proliferative glomerulonephritis. Of the 36 patients in whom distal tubular functions were evaluated, concentration and/or acidification defects were detected in 9 patients (25%). Renal histology revealed no abnormality in any of these patients. Serum C₃ levels were decreased in 5 patients with lepromatous leprosy and 3 patients with borderline leprosy.

Histological evidence of renal involvement was detected in 9 patients (15%). Amyloid deposits were seen in 3 (5%) patients of whom 2 had lepromatous leprosy and one had tuberculoid leprosy with chronic trophic ulcers. Mesangial proliferative lesions were seen in 5 (8.3%) and diffuse proliferative lesions (with crescents in more than 70% of glomeruli) in one patient. All of them had lepromatous leprosy. Three of the 5 patients with mesangial proliferative glomerulonephritis had erythema nodosum leprosum at the time of biopsy. Immunofluorescence studies revealed granular deposits of IgA, IgM and C₃ in one patient with mesangial proliferation and IgA/IgM with or without C₃ in 3 more patients in whom renal histology was normal. Glomerulonephritis associated with lep-

rosy appears to be immune mediated but confirmation requires identification of lepra antigen in the glomerular immune complex deposits.

KEY WORDS: leprosy, amyloidosis, renal lesions, glomerulonephritis, tubular dysfunction.

Introduction

Renal lesions associated with leprosy were first described in 1937 by Mitsuda and Ogawa who also observed that renal failure was a frequent cause of death in their patients. Although such lesions in leprosy have been the subject of several autopsy and biopsy studies, their exact pathogenesis remains uncertain. Moreover, a wide variation in the incidence and type of histological lesions seen in the kidney has been reported from different geographical areas (Date and Johny, 1975; Date *et al.*, 1977; Editorial, 1975; Johny and Karat, 1971; Johny *et al.*, 1975; McAdam *et al.*, 1975). The present study describes the renal lesions in leprosy as seen in north Indian patients.

Material and methods

The study was performed on 60 consecutive unselected patients with leprosy. These included 32 patients with lepromatous leprosy, 20 patients with borderline leprosy and 8 patients with tuberculoid leprosy according to well-established criteria (Ridley and Jopling, 1966). Eight patients had erythema nodosum leprosum (ENL) at the time of investigation. There were 44 males. The patients' ages ranged from 16-63 years.

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TABLE 1. Clinical features, laboratory data and renal histology in 60 patients

Type of leprosy	Number of patients	ENL	Urinalysis		Renal failure	Renal biopsy		
			Proteinuria	Microhaematuria		Amyloidosis	GN	Immunoglobulins/C ₃
Lepromatous	32	8	7	4	1	2	6	4
Borderline	20	0	0	0	0	0	0	0
Tuberculoid	8	0	1	0	0	1	0	0

ENL = Erythema nodosum leprosum, GN = Glomerulonephritis.

Urinalysis, including estimation of 24-hr protein excretion, was done in all patients. Blood urea, serum creatinine, serum complement (CH₅₀ and C₃) and antistreptolysin O titres were also estimated. In addition, CH₅₀ was measured in 227 and C₃ in 28 age-matched controls. Serum CH₅₀ was determined by the technique of Kabat and Mayer (1961) and C₃ by the immunoadherence method of Yonemasu and Inoue (1968). A test for antinuclear factor was done to exclude systemic lupus erythematosus. Distal tubular functions were assessed in 36 of these 60 patients. Urine concentrating ability was tested by measuring urine osmolality after 18 hr of fluid deprivation and failure of the urine osmolality to rise above 800 mOsm/kg was considered abnormal. The ammonium chloride loading test of Wrong and Davies (1959) was performed to test urinary acidification.

Kidney tissue was obtained in all patients by percutaneous biopsy and stained with haematoxylin and eosin, PAS, Congo Red and Thioflavin T. Immunofluorescence studies were done in 10 patients. Circulating immune complexes were also measured by a C₁q binding technique in these 10 patients.

Results

Urinalysis revealed proteinuria in 8 patients and microscopic haematuria in 4 patients. Quantitative estimation showed that the 24-hr protein excretion ranged from 0.4 g to 8.9 g in these 8 patients. The blood urea and creatinine levels were elevated in only one patient. The clinical features, biochemical data and renal histological findings are shown in Table 1.

On renal biopsy, specific lesions were detected in 9 patients (15%). The most common lesion was mesangial cell proliferation (Fig. 1), which was observed in 5 patients (8.3%). In one of these, there were areas of sclerosis in the glomeruli as well. Three of these patients had erythema nodosum leprosum at the time of biopsy. Diffuse proliferative glomerulonephritis with crescents in 70% of glomeruli (Fig. 2) was found in one patient. Glomerulonephritis was not found in any patient with borderline or tuberculoid leprosy. Amyloid deposits (Fig. 3) were found in 3 patients

(5%) of whom 2 had lepromatous leprosy and one had tuberculoid leprosy with chronic trophic ulcers. In 2 of these, the amyloid deposits were heavy both in the glomeruli as well as in the blood vessels and the interstitium whereas in the 3rd patient, the glomeruli and blood vessels showed only fine deposits. In 2 other patients, hyalinization of the arterioles was seen but was thought to be unrelated to leprosy. Interstitial nephritis was not found in any patient.

FIG. 1. Glomerulus showing diffuse mesangial cell proliferation H.E., $\times 345$.

Immunofluorescent microscopy revealed granular mesangial deposits of IgM, IgA and C₃ in one of the patients in whom mesangial proliferation was noted on light microscopy. Immunofluorescent studies in 9 other patients who exhibited no abnormalities on light microscopy showed deposits of IgA and C₃ in one patient, IgM and C₃ in another, and IgA alone in one patient. Of these 10 patients, 5 had significant levels of circulating immune complexes.

Clinically overt renal disease was present in only 4 patients. These included 3 patients who presented with a nephrotic syndrome and were found to have renal amyloidosis and one patient who was admitted with renal failure associated with crescentic glomerulonephritis. No patient had hypertension. Of the 3 patients with renal amyloidosis, no patient had tuberculosis or any disease other than leprosy which could have resulted in amyloidosis. Abnormalities on

FIG. 2. Photomicrograph showing diffuse mesangial cell proliferation and a prominent epithelial crescent in a glomerulus, H.E., $\times 345$.

FIG. 3. Photomicrograph showing amyloid deposits in the glomeruli, H.E., $\times 157$.

urinalysis were detected in 8 of the 9 patients who had specific renal lesions. The antistreptolysin O titre was not elevated in any of these patients.

The CH_{50} levels were decreased (normal range 32–50 haemolytic units) in 6 patients with lepromatous and 5 patients with borderline leprosy. The C_3 levels were decreased (normal range 84–160 mg/dl) in 5 patients of lepromatous leprosy (of whom 4 were in ENL) and 3 patients with borderline leprosy.

Of 36 patients in whom distal tubular functions were assessed, 9 patients (25%) were found to have

defects of concentration and/or acidification (Table 2). Of these, 4 patients had both defective concentrating ability and acidification, 3 patients had only a concentrating defect and 2 patients had defective acidification alone. No renal lesions was detected on histology in any of these patients.

Discussion

The incidence of secondary amyloidosis in leprosy has been observed to vary widely in different countries. In both autopsy and biopsy studies from the U.S.A., amyloidosis was detected in one-third of all patients (Powell and Swan, 1955; Shuttleworth and Ross, 1956; Williams *et al.*, 1965). Most of the patients investigated in these studies had lepromatous leprosy. Bernard and Vazquez (1973) from Argentina in an autopsy study of patients of lepromatous leprosy similarly reported a 31.2% incidence of renal amyloidosis. However, the incidence has been considerably lower in other areas. Williams *et al.* (1965) performed gingival biopsies in 118 patients in Mexico and found amyloidosis in only 3.3%. McAdam *et al.* (1975) reported an incidence of 8.4% from Papua New Guinea on the basis of rectal biopsies and a 2.4% incidence was noted in Malawi (Editorial, 1975). Amyloidosis was found in 5% of patients in the present study which is similar to the 0–8.1% incidence recorded in other studies from India (Desikan and Job, 1968; Gupta *et al.*, 1977; Gupta *et al.*, 1981; Johnny and Karat, 1971; Krishnamurthy and Job, 1966; Mittal *et al.*, 1972; Sainani and Rao, 1974).

Although amyloidosis does occasionally occur in association with tuberculoid leprosy in patients who have chronic trophic ulcers as seen in one of our patients, it is much more frequent in lepromatous leprosy (Date *et al.*, 1977; Editorial, 1975; McAdam *et al.*, 1975). Several workers have noted a striking association between repeated episodes of erythema nodosum leprosum (ENL) and the subsequent development of amyloidosis (Atta *et al.*, 1977; Date *et al.*, 1977; Editorial, 1975; McAdam *et al.*, 1975; Ramanujam *et al.*, 1973). In one study, all 5 patients who had suffered more than 20 episodes of ENL had amyloidosis (McAdam *et al.*, 1978).

A proliferative glomerulonephritis has been reported to occur both in the absence and presence of

TABLE 2. Distal tubular function defects in leprosy

Type of leprosy	Number of patients investigated	Renal histology	Concentrating defect	Acidification defect
Lepromatous	20	Normal	4	4
Borderline	13	Normal	3	2
Tuberculoid	3	Normal	0	0

an ENL reaction by several investigators (Bernard and Vazquez, 1973; Cologlu, 1979; Date and Johny, 1975; Date *et al.*, 1977; Drutz and Gutman, 1973; Gupta *et al.*, 1981; Iveson *et al.*, 1975; Johny and Karat, 1971; Johny *et al.*, 1975; Mittal *et al.*, 1972; Peter *et al.*, 1981). Proliferation may be focal or diffuse and most frequently involves the mesangial cells. Epithelial proliferation is relatively uncommon (Bedi *et al.*, 1977; Cologlu, 1979; Mittal *et al.*, 1972). The reported incidence of glomerulonephritis ranges from 13–61% and is higher in the lepromatous variety (Cologlu, 1979; Date and Johny, 1975; Date *et al.*, 1977; Gupta *et al.*, 1981; Johny *et al.*, 1975; Sainani and Rao, 1974). The considerably lower incidence of glomerulonephritis observed in this study is probably due to the inclusion of borderline and tuberculoid patients. The few ultra-structural studies done so far have revealed electron dense deposits mainly in a sub-endothelial and intramembranous location and rarely in the sub-epithelial region (Bullock, Callera and Panner, 1974; Cologlu, 1979; Date and Johny, 1975; Date *et al.*, 1977).

Circulating immune complexes and a fall in complement levels have been demonstrated frequently during ENL and occur in lepromatous leprosy even in the absence of ENL though less frequently (Bjorvatn *et al.*, 1976; Date *et al.*, 1977; Iveson *et al.*, 1975; Moran *et al.*, 1972; Shwe, 1972b; Shwe, 1972c; Shwe and Petty, 1972). These observations, coupled with the findings of deposits of immunoglobulins and complement in the glomeruli in some patients (Iveson *et al.*, 1975; Shwe, 1972a) as also observed in the present study, suggest that the glomerulonephritis is immune complex mediated. However, confirmation of this pathogenetic mechanism would require identification of lepra antigens in the glomeruli and the elution of specific antibody.

Distal tubular function defects were observed in 25% of patients in the present study. A similar incidence of 29% was reported by Gutman *et al.* (1973). Although interstitial nephritis has also been described in leprosy by some workers (Bernard and Vazquez, 1973; Gupta *et al.*, 1977; Mittal *et al.*, 1972; Sainani and Rao, 1974; Shwe, 1972a) several others have recorded the total absence of any interstitial lesions (Date *et al.*, 1977; Gupta *et al.*, 1981; Johny and Karat, 1971; Peter *et al.*, 1981). The impairment in concentrating ability and acidification is difficult to explain in the absence of any such lesions.

Renal failure is a frequent cause of death in leprosy (Bernard and Vazquez, 1973; Brusco and Masanti, 1963; Desikan and Job, 1968; Kean and Childress, 1942; Powell and Swan, 1955) and since ENL is frequently associated with both glomerulonephritis and amyloidosis, a reduction in the frequency of ENL could be expected to reduce the incidence of renal complications. ENL reactions are much less

frequent when dapsone and clofazimine are used in combination than when dapsone is used alone (Yawalkar and Vischer, 1979), and therefore, this combined drug regimen should be preferred particularly in lepromatous leprosy.

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(Accepted 21 March 1983)