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Immunofluorescence characterization of light chains in human nephropathies

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Summary. Renal tissue from 185 patients with various nephropathies were studied by immunofluorescence, in order to look for the frequency and potential predominance of kappa or lambda light chain glomerular deposits. Four normal renal biopsies were used as controls. An overall study shows that light chains were present in glomeruli in 136 out of 185 cases; kappa light chain deposits were more frequent than lambda light chain deposits (73,5% and 64,3% respectively). An analytical study shows that this was not observed in all nephropathies studied. In mesangial IgA nephropathy, lambda light chain deposits were seen in 81% of cases (29 out of 37) and kappa light chain deposits were observed in 78% (30 out of 37 cases). In lupus nephritis, lambda light chain deposits were present in 13 out of 14 cases (92,8%) whereas kappa light chain deposits were demonstrated in 12 cases (85,7%). In other nephropathies such as membranous, endocapillary proliferative and amyloid nephritis, kappa was the predominant light chain observed in glomeruli or was present in the same number of cases as lambda light chain (mesangiocapillary glomerulonephritis). These findings show that in certain nephritides, for example IgA nephropathy and lupus nephritis, IgA and IgG deposits are mainly composed of lambda light chain in contrast with the normal kappa:lambda ratio in human serum of 2:1.

Key words: Immunofluorescence – Light chains – Nephropathies.

Introduction

The presence of light chain deposits in renal tissue has been generally demonstrated in cases of light chain nephropathy and in multiple myeloma (Randal et al. 1976; Seymour et al. 1980; Alpers et al. 1983). In patients without overt myeloma and without any clinical or biological evidence of monoclonal gammopathy, the presence of light chain deposits in kidney tissue has been reported by some authors (Herdman et al. 1967; Soda and Yinoshita 1978).

More recently Lai et al. (1986) demonstrated that mesangial IgA deposits in IgA nephropathy consist mainly of lambda light chain. In human serum the normal ratio of kappa:lambda light chain of immunoglobulins is two to one (Stone 1982). We considered that it would be interesting to determine whether this ratio is demonstrated in human nephropathies.

In the present study, we report our immunofluorescence findings using monospecific anti-kappa and anti-lambda light chain antisera in 185 cases with various nephropathies. As controls, specimens of cadaveric normal kidneys not used for transplantation were studied, using the same antisera.

Materials and methods

We studied renal biopsies from 4 brain death patients with normal non-transplanted kidneys and from 185 patients with various nephropathies.

Renal biopsy was obtained by percutaneous or open biopsy. Each specimen was divided into three parts. The first part was fixed in Dubosq-Brazil solution and embedded in paraffin. The sections were stained with haematoxylin and eosin, periodic acid-Schiff reagent and Masson's trichrome.

The second part was rapidly placed in OCT compound (Ames Tissues Teck Miles, Labs, Naperville, Ill) and frozen in liquid nitrogen. Frozen sections cut at 3 μm were examined by direct immunofluorescence with commercial antisera against human IgM, IgA, C3 (Hyland Division Travenol Labs, Inc, Deerfield, Ill) IgG, Clq, C4 fibrinogen, apo-lipoprotein B, albumin (Behringwerke, Marburg, FRG), kappa light chain and lambda light chain (Meloy Laboratories and Dakopatts a/s, Glostrup, Denmark). These antisera were conjugated with fluo-

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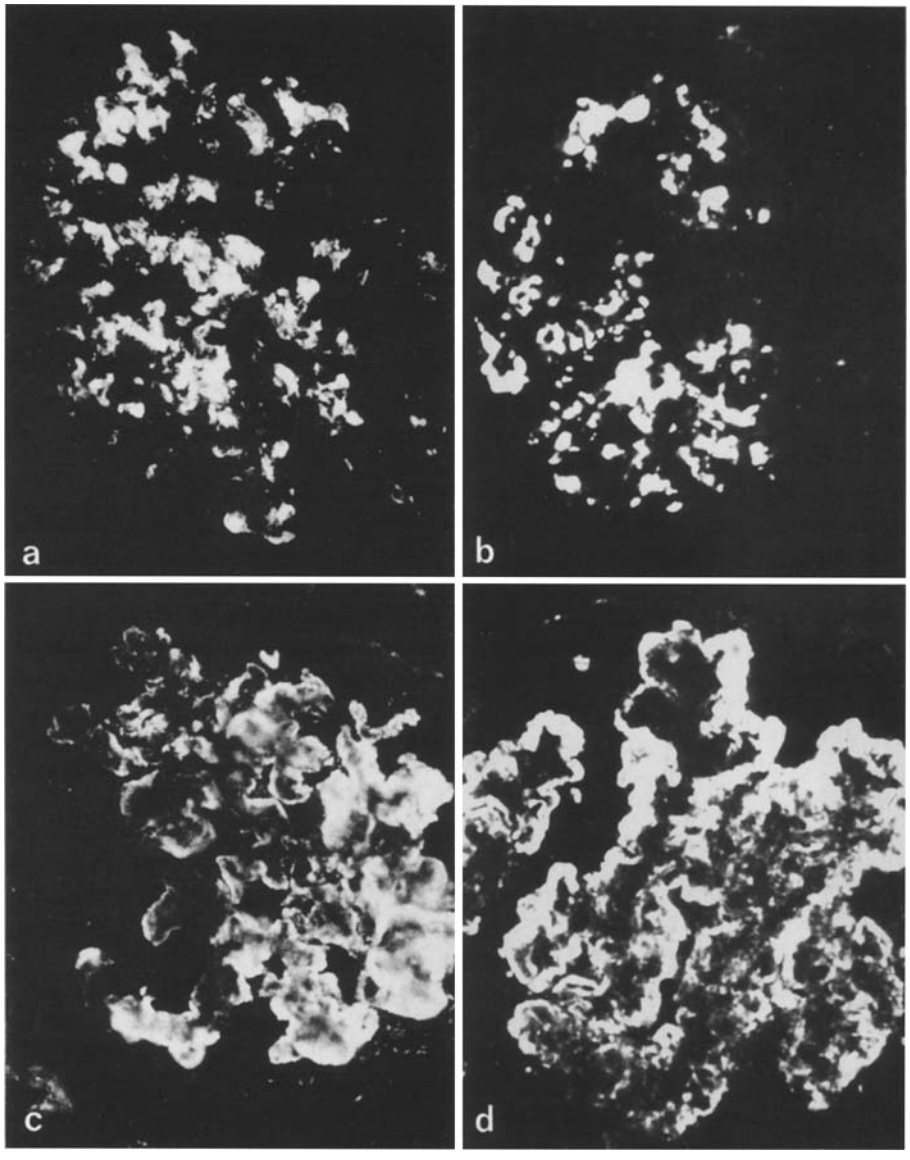

Fig. 1. Immunofluorescence staining with FITC antiserum. **a** IgA nephropathy: mesangial staining. Anti-lambda (×350). **b** IgA nephropathy: mesangial staining. Anti-IgA. Same patient as a (×350). **c** Lupus nephritis: granular staining along glomerular basement membrane and mesangium. Anti-lambda (×350). **d** Lupus nephritis: granular staining along glomerular basement membrane and mesangium. Anti-IgG. Same patient as **c** (×350).

Table 1. Presence of immunofluorescence light chain deposits in some nephropathies.

Diagnosis	Glomerular deposits			
	λ Alone (*n*)	Associated $\varkappa+\lambda$ (*n*)	$\varkappa$ alone (*n*)	No light chains (*n*)
IgA nephropathy (37)	6	24	5	2
Lupus nephritis (14)	2	11	1	0
Mesangiocapillary GN (16)	3	7	3	3
Membranous GN (44)	3	33	8	0
AL amyloidosis (14)	1	9	2	2
AA amyloidosis (17)	0	5	6	6

rescein. The monospecificity of these antisera was tested by immunoelectrophoresis against normal human plasma and human serum. After staining, the sections were examined with a Leitz Dialux microscope with an HBO 50 light source.

For tests, some slides were treated with alcohol-ether (v/v) fixative before staining.

The third part was fixed in 4% glutaraldehyde, washed in HCl-cacodylate buffer, post-fixed in 2% osmium tetroxide and embedded in Epon 812. Thin sections were stained with uranyl acetate and lead citrate and examined in an OPL electron microscope.

No clinical features of immunocyte dyscrasia were present in this group. Serum electrophoresis and immunoelectrophoresis were performed in patients and revealed no monoclonal gammopathy or myeloma. Immunoelectrophoresis of urinary concentrate demonstrated no Bence-Jones proteins or immunoglobulin fragments such as isolated heavy chains.

Results

Overall study showed that kappa light chain deposits were observed in 136 out of 185 cases (73,5%) and lambda light chains were present in 119 out of 185 cases (64,3%) in glomeruli. Thirty two cases were monotypic for kappa and 20 cases for lambda light chain. In 31 cases no light chain deposits were present.

No differences were present when the sections were treated with or without fixation.

By light and electron microscopy, the changes observed in nephropathies were characteristic for each diagnostic category. The immunofluorescent findings are summarized in Table 1. An analytical and detailed study was limited to two types of nephropathy, IgA and lupus nephritis.

In normal kidneys (4 cases), no light or heavy chain deposits were observed. In IgA nephropathy (37 cases), kappa light chain deposits were present in mesangium in 29 cases; lambda light chain deposits were observed in 30 cases. In 9 cases, the intensity of fluorescence for lambda light chain was greater than that for the kappa light chain. In 6 cases there was no demonstrable fluorescence with anti-kappa and in 5 cases with anti-lambda. No positivity was observed in 2 cases. In lupus nephritis (14 cases) lambda light chain deposits were present in mesangium and along glomerular basement membranes in a granular pattern in 13 cases (92,8%) whereas kappa light chain was observed in 85,7% (12 out of 14 cases). Lambda light chain deposits were more intense in 4 cases and isolated in 2 cases.

In other types of nephropathy a similar number of cases presented deposits of light chains to the numbers seen in mesangiocapillary glomerulonephritis; kappa light chain deposits were more frequently observed in membranous, endocapillary proliferative and amyloid nephritis.

Discussion

In the literature, light chain deposits have been demonstrated in renal tissue from patients with multiple myeloma or light chain nephropathy (Randal et al. 1976; Seymour et al. 1980) and in patients with various nephropathies (Herdman et al. 1967; Soda and Yinoshita 1978; Lai et al. 1986).

In our study, we have demonstrated the presence of light chain glomerular deposits in 73,5% of cases. The kappa light chain was predominant in our overall study, but in certain nephropathies, lambda light chain deposits were slightly more frequently observed. In IgA nephropathy this has already been demonstrated by Lai et al. (1986) who noticed this predominance only in this nephropathy. We have found that in lupus nephritis, lambda light chain was also slightly more predominant in agreement with Soda and Yinoshita (1978) who noticed that "deposits in systemic lupus erythematosus were predominantly positive for lambda chain".

The pathogenesis of light chain deposits is uncertain. It has been shown that the kidney is the major site of catabolism for them they must first pass through the glomerular filter and are then catabolized and reabsorbed by tubular epithelial cells, unless tubular disease or an excess of filtered protein prevent reabsorption (Waldmann et al. 1972; Strober et al. 1974). The possibility of an impairment of tubular reabsorption seems unlikely since none of the patients studied here had light chains in their urine.

The mechanisms of light chain accumulation in renal tissue is unclear: increasing concentration of light chains in serum and tubules has been described in chronic renal failure (Strober et al. 1974). In casts, the presence of light chains associated with other proteins such as Tamm-Horsfall mucoprotein (Mc Kenzie and Mc Queen 1969) may explain the renal failure observed in cases with such cast formation in myeloma kidney (Rao et al. 1968; Cohen et al. 1981). The renal toxicity of light chains could be caused by their obstructive effect when they combine with proteins such as Tamm-Horsfall mucoprotein, this combination depending of their isoelectric point.

Another question concerns the specificity of the deposition of glomerular light chain. Is this deposition, only a reaction following glomerular filtration?

In nephropathies, it seems that light chain deposits are not a nonspecific deposition. Herdman et al. (1967) after comparison of light chain deposi-

tion and the immunoglobulin (Ig) pool of peripheral blood concluded that Ig's located in the kidney are derived from antibody and not from the Ig pool. Moreover, some physicochemical properties of the light chains, such as their isoelectric point, might be critical in their deposition but this has not been investigated in our study.

We have seen that in some cases, there were deposits of only one light chain. It seems that this deposit corresponded to a clone of plasma-cells producing Ig of only one light chain type (Bernier and Cebra 1965) after selective stimulation. The specific Ig was observed in the kidney (Herdman et al. 1967).

It has been shown that the normal serum $\varkappa:\lambda$ ratio is about 2:1 (Stone 1982). This could explain the predominant and intense kappa light chain staining observed in our patients. The reason why this ratio is altered in some nephropathies such as IgA nephropathy and lupus nephritis is unclear. The production of one light chain (lambda in these cases) rather than the other could be induced by a specific immune response to a particular antigen and it ensures specific deposition of lambda light chain in the kidney.

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