Fundus changes in mesangiocapillary glomerulonephritis type II: clinical and fluorescein angiographic findings

J DUVAL-YOUNG,¹ C D SHORT,² M F RAINES,¹ R GOKAL,² AND W LAWLER³

From the ¹Department of Ophthalmology, ²Department of Renal Medicine, and ³Department of Pathology, University of Manchester.

SUMMARY Previously we have demonstrated a deposit in Bruch's membrane in a single case of mesangiocapillary glomerulonephritis type II. We studied a group of patients with this disease and described extensive clinical and fluorescein angiographic abnormalities, which were in marked contrast to the findings in a group of patients with other forms of glomerulonephritis. This finding contributes to our understanding of the pathophysiology of the complex of the retinal pigment epithelium, Bruch's membrane, and choriocapillaris.

A comparison can be made between the anatomy of the glomerulus and the choriocapillaris-Bruch's membrane-retinal pigment epithelium complex, in which the choriocapillaris is likened to the glomerular tuft, Bruch's membrane to the glomerular basement membrane, and the retinal pigment epithelium to the glomerular epithelium.¹

In a previous case report of a patient with type II mesangiocapillary glomerulonephritis (MCGN) we have demonstrated the occurrence of deposits in the choriocapillaris and Bruch's membrane which have the clinical appearance of drusen but the histopathological characteristics of deposits in the glomerulus.² In type II MCGN, which is frequently associated with partial lipodystrophy (PLD), deposits of electron dense material, often with a ribbon like appearance, are found within the glomerular basement membrane.³ This is in contrast to the discrete deposits found in (a) membranous nephropathy, where the material lies initially between the basement membrane and the epithelium; (b) in type I MCGN, where the deposit is predominantly sub-endothelial between the basement membrane and the endothelium; and (c) in mesangial proliferative glomerulonephritis, where the majority of the deposits are in the mesangium⁴ (Fig. 1).

We have therefore examined clinically the eyes of

patients with a variety of glomerular disorders, including further cases of type II MCGN and partial lipodystrophy (PLD), and report our findings.

Methods and patients

From the diagnostic index at the Manchester Royal Infirmary Renal Unit we selected for ophthalmic investigation 17 patients with biopsy proved glomerular disease and two further patients with PLD but who had never had a renal biopsy. The histological diagnosis was withheld from the ophthalmologists who examined the patients by routine clinical methods, fundus photography, and fundus fluorescein angiography. All the patients were normotensive and had been so for some months, though many had had a period of hypertension earlier in the course of their illness. Patients 4, 7, and 13 had reached end stage renal failure and had had successful renal transplantation at the time of the study. No patient was receiving dialysis.

Details of the patients are given in Tables 1, 2, and 3.

Results

None of the patients had ocular symptoms. All the anterior segments appeared normal and no hypertensive retinopathy was detected.

Correspondence to J Duvall-Young, FRCS, Walton Hospital, Rice Lane, Liverpool L9 1AE.

Fig. 1 Predominant sites of deposition of immunoreactive and electron-dense material in various glomerulopathies.

Of the 12 patients without PLD six had type I MCGN, one had minimal change disease (a term used by renal pathologists to describe a nephritis in which there is no evidence of disease on light microscopy), and five had membranous nephropathy.

Table 1 Clinical details of cases with PLD

Case	Age (yr)	Sex	Glomerular disease	Time since diagnosis (yr)	Blood pressure (mm Hg)	Current medication
1	43	M	MCGN II	0.6	140/90	Tenoretic
2	45	F	MCGN (type unknown)	27	135/90	Nifedipine Hydralazine Atenolol Methyldopa Bendrofluzide
3	28	F	MCGN II	24	130/80	Cyclosporin Atenolol
4	36	M	MCGN II	2.2	150/85	Allopurinol Captopril Frusemide
5	30	F	Nephrotic syndrome: no biopsy	14	150/80	Cyclosporin Prednisolone Atenolol
6	43	F	No biopsy: normal renal function		110/70	Anxiolytics
7	43	M	MCGN II	31	115/70	Tenoretic

Tenoretic=atenolol 100 mg and chlorthalidone 25 mg.

Ophthalmoscopic examination of these eyes revealed a few drusen (Fig. 2), but with no difference in

Table 2 Clinical details of cases without PLD

Case	Age (yr)	Sex	Glomerular disease	Time since Diagnosis (yr)	Blood pressure (mm Hg)	Current medication
8	51	M	Membranous	2	180/100	Prednisolone Atenolol Nifedipine
9	31	M	MCGN I	6	140/90	Nil
10	43	F	MCGN I	9	140/85	Nil
11	44	F	MCGN I	6	160/90	Azathioprine Prednisolone Atenolol
12	73	M	Membranous	5	140/70	Nil
13	49	F	MCGN I	1	180/95	Prednisolone Azathioprine Atenolol Nifedipine
14	39	M	Membranous	6	125/90	Bendrofluzide
15	32	M	Membranous	2	140/90	Prednisolone Frusemide Spironolactone
16	25	F	MCGN I	1.5	150/90	Nil
17	50	M	MCGN I	13	160/90	Methyldopa Frusemide Propranolol
18	29	F	Minimal change	3	90/60	Nil
19	50	F	Membranous	7	130/80	Nil

Table 3 Summary of patients

With partial lipodystrophy		Without partial lipodystrophy	
Type II MCGN	4	Type I MCGN	6
MCGN unclassified	1	Minimal change	1
End stage renal failure	1	Membranous	5
No renal lesion	1		
Total	7		12

frequency from that expected in normal age matched population. Similarly the fluorescein angiograms showed only a few hyperfluorescent spots corresponding to scattered drusen.

Of the seven patients with PLD (Table 4) five were found to have a very striking abnormality in the fundi (Figs. 3,4,5). There was a regular, bilaterally symmetrical distribution of discrete yellow spots, similar to drusen, more densely present posteriorly but spreading up to and beyond the equator. The lesions were not elevated, but were associated with some 'irregularity' of pigmentation. In the same five patients fluorescein angiography showed gross abnormalities correlating with the drusen-like appearance, and similar to that seen in the previous case report,² with hyperfluorescence corresponding to the yellow lesions but with no leakage of fluorescein. There was some variation from case to case in the dimensions and distribution of the deposits, but there was symmetry within each case. The visual acuity was unaffected. Four of these five cases had biopsy proved type II MCGN, and the fifth was likely to be in this category on the basis of PLD and nephrotic syndrome, though no biopsy was ever taken.

Two patients with PLD had normal ophthalmoscopic and angiographic appearances. One had unclassified MCGN, and the other had no evidence of glomerular disease.

Table 4 Ophthalmic findings in cases with PLD

Case	Visual acuity		Fundus examination	Fluorescein angiography
	R	L		
1	6/6	6/9	Massive drusen-like deposits and mottled pigmentation	Extensive hyperfluorescence in Bruch's membrane
2	6/6	6/5	Drusen-like deposits and mottled pigmentation	Few corresponding hyperfluorescent spots over drusen
3	6/6	6/6	Massive drusen-like deposits and mottled pigmentation	Extensive hyperfluorescence
4	6/9	6/9	Massive drusen-like deposits and mottled pigmentation	Extensive hyperfluorescence
5	6/36	6/24	Massive drusen-like deposits and mottled pigmentation	Extensive hyperfluorescence
6	6/6	6/6	Normal	Normal
7	6/5	6/5	Massive drusen-like deposits and mottled pigmentation	Extensive hyperfluorescence in Bruch's membrane

Fig. 2 Fundus photograph of case 18 showing scattered drusen at the posterior pole.

Discussion

We have described for the first time, to our knowledge, in this and in our recent publication² an abnormal deposit in the eye at the level of Bruch's membrane and choriocapillaries in type II mesangiocapillary glomerulonephritis. Our findings in this communication support the hypothesis that the choriocapillaris - Bruch's membrane - retinal pigment epithelial complex may respond to disease in a similar way to the glomerulus.

The previously reported fundus changes seen in glomerular disease can be broadly divided into those associated with hypertension, those associated with vasculitis causing glomerulonephritis, those resulting from treatment of the renal lesion, and those

Fig. 3A

Fig. 3B

Fig. 3C

Fig. 3 A: Fundus photograph and B, C, fluorescein angiogram of case 4 showing large posterior pole deposits with a pigmented halo temporal to the macula, associated with intense focal hyperfluorescence which extends towards the equator.

considered to be specifically related to the renal lesion.⁵ In systemic hypertension the fundus abnormalities are well recognised, and they are described in renal patients. In accelerated hypertension infarcts of the retinal pigment epithelium, corresponding to failure of lobules of choriocapillaris to be perfused, termed Elschnig's spots, are described,⁶ but they

differ from the lesions we report in that they are much more widespread and are not associated with the focal pigment clumping seen in Elschnig's spots. In addition there is no history of visual disturbance in any of our patients, whereas if there were such widespread infarction of the retinal pigment epithelium visual symptoms would be expected.

A series of patients with glomerulonephritis with and without hypertension have been studied ophthalmoscopically.⁷ None of these showed any fluorescein angiographic abnormality, though the type of glomerulonephritis was not identified.

Vasculitis, such as is seen in systemic lupus erythematosus, may involve the renal circulation as well as the retinal and choroidal circulation, giving rise to cotton-wool spots, haemorrhages, swelling of the optic nerve head, and vascular occlusion.⁸⁻¹² In the cases we have studied no features of vasculitis were present.

Ocular complications of chronic renal disease involve exudative retinal detachment¹³ and crystals of cystine in the cornea and retina,¹⁴ and the complications of treatment include cataract, raised intraocular pressure, opportunistic retinitis,¹⁵ and retinal microaneurysms.¹⁶

A number of familial disorders are described which affect the eye and kidney. Those which involve the retina and choroid include Alstrom's syndrome,¹⁷⁻²⁰ which comprises pigmentary retinopathy, obesity, diabetes mellitus, and nerve deafness, often associated with renal insufficiency; Alport's syndrome,²¹⁻²³ which is characterised by lenticonus, spherophakia, sensorineural deafness, and a hereditary nephropathy and sometimes pigmentary

Fig. 4A

Fig. 4B

Fig. 4 A: Fundus photograph and B. fluorescein angiogram of case 10 showing scattered drusen-like deposits with intense hyperfluorescence.

retinopathy with or without subretinal and Bruch's membrane deposits; and adult polycystic kidney disease.²⁴ A miscellaneous group of hereditary renal lesions associated with other fundus abnormalities, usually manifest as pigmentary retinopathies, are described.²⁵⁻²⁹ The only previous publications comparing pathology of the kidney and eye refer to

patients with diabetes mellitus: microaneurysms have been described in the glomerulus³⁰ and lesions resembling Kimmelsteil-Wilson nodules were described in the choroid.³¹

Bruch's membrane and the glomerular membrane are structurally homologous in that both are selectively and directionally permeable,³²⁻³⁴ with a positive

Fig. 5A

Fig. 5B

Fig. 5 A: Fundus photograph and B. fluorescein angiogram of case 19 showing extensive drusen-like deposits with hyperfluorescence.

charge and a high heparan sulphate content.³⁵⁻³⁶ The two membranes differ in that the collagenous zones of Bruch's membrane make it much thicker than the glomerular basement membrane. Pathological changes in the renal glomerular basement membrane with similarities to those seen in Bruch's membrane are identifiable. In aging, the glomerular basement membrane is focally thickened, with the appearance of vesicles in the membrane³⁷ similar to the aging changes of Bruch's membrane.³⁸ In aminoglycoside nephrosis, deposits with an ultrastructural similarity to drusen are present on the epithelial side of the glomerular basement membrane.³⁹ Aminoglycoside toxicity has been used as an experimental means of creating drusen in the eye.⁴⁰ Breaks in the glomerular basement membrane, reminiscent of angiod streaks in Bruch's membrane, have also been described.⁴¹

The nature of deposits in different types of glomerulonephritis differs histologically and presumably also pathogenetically. We suggest that, whatever the pathogenesis in MCGN type II, a similar setting pertains in Bruch's membrane, whereas in the other forms of glomerulonephritis this may not be the case. Recently an early case of MCGN II has been studied histopathologically.⁴² It is interesting that the early lesion prior to the appearance of the dense deposit is lamellation of the lamina densa of the glomerular basement membranes, very reminiscent of the appearance seen in Alport's syndrome,⁴³ which is undisputably associated with a chorioretinal lesion.⁴⁴⁻⁴⁵

Our findings suggest that, in patients with type II MCGN and PLD, chorioretinal changes similarly may parallel those found in the kidney. Although in all five patients with PLD and fundus changes the ophthalmic findings were very similar, the duration of renal disease ranged from 7 months to 31 years, and sequential observation is necessary to determine whether a lesion is static or variable with time. There is undoubtedly a structural and a pathological comparison to be drawn between the eye and the kidney, and further investigation of patients with glomerular disease may well shed light on the pathophysiological responses of the complex of choriocapillaris, Bruch's membrane, and retinal pigment epithelial. Similarly, study of the ocular responses may contribute to the understanding of the pathogenesis of the renal lesion.

References

- Duval J, Tso MOM. Cellular mechanism of resolution of drusen after laser coagulation. An experimental study. *Arch Ophthalmol* 1985; **103**: 694-703.
- Duval-Young J, MacDonald MK, McKechnie NM. Fundus changes in (type II) mesangiocapillary glomerulonephritis simulating drusen: a histopathological report. *Br J Ophthalmol* 1989; **73**: 297-302.
- Churg J, Duffy JE, Bernstein J. Identification of dense deposit disease. *Arch Pathol Lab Med* 1979; **1403**: 67-72.
- Hepstinal RH. *Pathology of the kidney*. 2nd ed. Boston: Little, Brown, 1974.
- Easterbrook M, Mortimer CB. Ocular signs in chronic renal failure. *Br J Ophthalmol* 1970; **54**: 724-30.
- Klien BA. Ischaemic infarcts of the choroid. *Am J Ophthalmol* 1969; **66**: 1069-74.
- Miyake K, Maeda K, Imai T, et al. Vitreous fluorophotometry in diseased blood retinal barriers III. Chronic glomerulonephritis part 1. *J Clin Ophthalmol (Japan)* 1981; **35**: 53-9.
- Cordes FC, Aitken SD. Ocular changes in acute disseminated lupus erythematosus. *Am J Ophthalmol* 1947; **30**: 1541-55.
- Bishko F. Retinopathy in systemic lupus erythematosus. A case report and review of the literature. *Arthritis Rheum* 1972; **15**: 57-63.
- Henkind P. Fundus lesions in connective tissue disease. *Trans Ophthalmol Soc UK* 1974; **94**: 785-806.
- Lanham JG, Barrie T, Kohner EM, Hughes GRVG. SLE retinopathy: evaluation by fluorescein angiography. *Ann Rheum Dis* 1982; **41**: 473-8.
- Jabs DA, Fine SL, Holchberg MC, Newman SA, Heiner GG, Stevens MB. Severe retinal vaso-occlusive disease in systemic lupus erythematosus. *Arch Ophthalmol* 1986; **104**: 558-63.
- Buchanan WS, Ellis PP. Retinal separation in chronic glomerulonephritis. *Arch Ophthalmol* 1964; **71**: 182-6.
- Kaiser-Kupfer MI, Camiso RC, Mincler DS, Gahl WA. Long term ocular manifestations of nephropathic cystinosis. *Arch Ophthalmol* 1986; **104**: 706-11.
- La Piana FG. Renal disease in clinical ophthalmology. In: Duane TD, Jaeger EA, eds. Philadelphia: Harper and Row, 1982; **5**: ch 31.
- Hayasaka S, Kitaoka M, Mizunok K. Peripheral retinal microaneurysms in patients receiving hemodialysis. *Retina* 1986; **6**: 113-8.
- Alstrom CH, Hallgren B, Nilsson CB. Retinal degeneration combined with obesity, diabetes mellitus and neurogenous deafness. A specific syndrome (not hitherto described) from the Laurence-Moon-Barlet-Beedl syndrome. *Acta Psychiatr Scand* 1959; **34** (suppl): 129.
- Millay RH, Weleber RG, Heckenlively JR. Ophthalmic and systemic manifestations of Alstrom's disease. *Am J Ophthalmol* 1986; **102**: 482-90.
- Sebag J, Albert DL, Craft JL. The Alstrom syndrome. Ophthalmic, histopathologic, and renal ultrastructure. *Br J Ophthalmol* 1984; **68**: 494-501.
- Goldstein JL, Fialkow PJ. The Alstrom syndrome. Report of three cases with further delineation of the clinical, pathophysical and genetic aspects of the disorder. *Medicine* 1973; **52**: 53-91.
- Purriez P, Drets M, Pascale E, et al. Familial hereditary nephropathy (Alport's syndrome). *Am J Med* 1971; **49**: 753-73.
- Davies PD. Pigment dispersion in a case of Alport's syndrome. *Br J Ophthalmol* 1970; **54**: 557-61.
- Peterson WS, Albert DM. Fundus changes in the hereditary nephropathies. *Ophthalmology* 1974; **78**: 762-71.
- Fairley KF, Leighton PW, Kinkaid-Smith P. Familial visual defects associated with polycystic kidney and medullary sponge kidney. *Br Med J* 1963; **i**: 1060-3.
- Loken AL, Hanssen O, Halvorsen S, Jolster NJ. Hereditary renal dysplasia and blindness. *Acta Paediatr Scand* 1961; **50**: 177-84.
- Senior B, Friedman AL, Braudou L. Juvenile familial nephropathy with tapetoretinal degeneration - a new oculo-renal dystrophy. *Am J Ophthalmol* 1961; **52**: 625.
- Bsgouni B, Lolo-Spada G, Biatti S. Tapetoretinal degeneration with marginal corneal dystrophy. *Am J Ophthalmol* 1968; **65**: 53-60.
- Schimke RN. Hereditary renal-retinal dysplasia. *Ann Intern Med* 1969; **70**: 735-44.

- 29 Edwards WC, Grizzard WS. Tapeto-retinal degeneration associated with renal disease. *J Pediatr Ophthalmol Strabismus* 1981; **18**: 55-7.
- 30 Nakamoto Y, Takazakura E, Hayakawa H, *et al*. Intraretinal microaneurysms in diabetic nephropathy. *Lab Invest* 1980; **42**: 433-9.
- 31 Hidayat AA, Fine BS. Diabetic choroidopathy: light and electron microscopy observation of seven cases. *Ophthalmology* 1985; **92**: 512-52.
- 32 Hogan MJ. Electron microscopy of Bruch's membrane. *Ophthalmology* 1965; **69**: 683-90.
- 33 Farquar MG. The primary glomerular filtration barrier-basement membrane or epithelial cells? *Kidney Int* 1975; **8**: 197-211.
- 34 Carlson EC, Kenney MC. Morphological heterogeneity of isolated renal basement membranes. *Renal Physiol* 1980; **3**: 288-97.
- 35 Pino RM, Essner E, Pino LC. Location and chemical composition of anionic sites in Bruch's membrane of the rat. *J Histochem Cytochem* 1982; **30**: 245-52.
- 36 Rennke HG, Cotran RS, Venkatachalam MA. Role of the molecular charge in glomerular permeability. Tracer studies with cationised ferritins. *J Cell Biol* 1975; **67**: 638-46.
- 37 Hayashide M, Yu BP, Masor EJ, Iwasaki K, Ikeda T. An electron microscopic examination of age related changes in the kidney. The influence of diet. *Exp Gerontol* 1986; **21**: 535-53.
- 38 Feeney-Burns L, Ellersieck MR. Age related changes in the ultrastructure of Bruch's membrane. *Am J Ophthalmol* 1985; **100**: 686-97.
- 39 Kurtz SM, Feldman JD. Experimental studies on the formation of the glomerular basement membrane. *J Ultrastruct Res* 1962; **6**: 19-27.
- 40 El Baba F, Green WR, Fleischmann J, Finklestein D, de la Cruz ZC. Clinicopathologic correlation of lipidisation and detachment of the retinal pigment epithelium. *Am J Ophthalmol* 1986; **101**: 576-83.
- 41 Terasaki T, Sano M, Narita M, Tojo S. Ultrastructural study of the gaps of the glomerular basement membrane in IgA nephropathy. *Am J Nephrol* 1986; **6**: 443-9.
- 42 Sato H, Santo T, Seino J, *et al*. Dense deposit disease: its possible pathogenesis suggested by the observation of a patient. *Clin Nephrol* 1987; **27**: 41-5.
- 43 Gubler M, Levy M, Broyer M, *et al*. Alport's syndrome. A report of 58 cases and a review of the literature. *Am J Med* 1981; **70**: 493-505.
- 44 Govan JAA. Ocular manifestation of Alport's syndrome. A hereditary disorder of basement membranes? *Br J Ophthalmol* 1983; **67**: 493-503.
- 45 Thompson SM, Deady JP, Willshaw HE, White RHR. Ocular signs in Alport's syndrome. *Eye* 1987; **1**: 146-53.

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