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Translational Mini-Review Series on Complement Factor H: Renal diseases associated with complement factor H: novel insights from humans and animals

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Summary

Factor H is the major regulatory protein of the alternative pathway of complement activation. Abnormalities in factor H have been associated with renal disease, namely glomerulonephritis with C3 deposition including membranoproliferative glomerulonephritis (MPGN) and the atypical haemolytic uraemic syndrome (aHUS). Furthermore, a common factor H polymorphism has been identified as a risk factor for the development of age-related macular degeneration. These associations suggest that alternative pathway dysregulation is a common feature in the pathogenesis of these conditions. However, with respect to factor H-associated renal disease, it is now clear that distinct molecular defects in the protein underlie the pathogenesis of glomerulonephritis and HUS. In this paper we review the associations between human factor H dysfunction and renal disease and explore how observations in both spontaneous and engineered animal models of factor H dysfunction have contributed to our understanding of the pathogenesis of factor H-related renal disease.

Keywords: complement, Factor H, glomerulonephritis, thrombosis

Biological function of complement factor H

Complement factor H was first described in 1965 [1]. It is an abundant, single chain glycoprotein circulating at a concentration of approximately 400 mg/l. The major source of factor H is the liver, but extra-hepatic synthesis has been demonstrated in a variety of tissues including endothelial cells [2], glomerular mesangial cells [3] and in rodents, podocytes [4]. The protein is composed of 20 short consensus repeat (SCR) domains, also known as complement control protein domains, or Sushi repeats. Each SCR domain is composed of approximately 60 amino acids based on a framework of four conserved cysteine residues.

The principle function of factor H is to down-regulate alternative pathway complement activation, which it achieves in three ways. It acts as an essential co-factor in the factor I-mediated proteolytic conversion of plasma C3b to iC3b [5,6]. iC3b may then be cleaved into further fragments (C3dg and C3c) by factor I using the membrane-bound co-factor CR1 (complement receptor 1, CD35). Factor H is also able to block the formation of the alternative pathway C3 convertases by binding to C3b, thereby inhibiting the interaction between C3b and factor B [7–10]. Factor H also possesses decay acceleration activity, i.e. promotes the dissociation of these C3 convertases once they have formed [8]. It is also able to distinguish between activator and non-activator surfaces *in vivo*, an effect mediated partly by its ability to bind sialic acid [11–13].

Deletion mutagenesis studies have demonstrated that regulation of fluid-phase C3 activation requires the N-terminal five SCR domains [14–16]. In contrast, targeting of the protein to cell surfaces (surface recognition function) is mediated by C-terminal domains [17]. That the complement regulatory and surface recognition functions reside in

distinct locations of the protein is of major importance in the understanding of the molecular pathogenesis of factor H-associated renal disease.

Age-related macular degeneration (AMD) [18–21], atypical haemolytic uraemic syndrome (HUS) (reviewed in [22]) and membranoproliferative glomerulonephritis (MPGN) [20,23–27] are associated with polymorphisms or mutations in the factor H gene. This suggested the existence of a genotype–phenotype relationship [28].

In the first section of this review we will discuss the renal pathology associated with factor H dysfunction and explore its similarities to the renal pathology described in other situations where alternative pathway dysregulation occurs. We start by reviewing the pathology described in individuals with homozygous factor H deficiency.

Human factor H deficiency associated with very low or absent factor H levels

The phenotypic analysis of individuals with inherited complete deficiency of factor H has provided important insights into the biological role of factor H *in vivo*. However, such cases are extremely rare; in Table 1 we summarize the clinical and laboratory investigations of 33 factor H-deficient individuals from 15 families [23,25–27,29–38]. In all these individuals factor H levels were absent or markedly reduced.

That factor H is the major regulator of alternative pathway activation *in vivo* is evident from the complement profile described in this deficiency state. Typically, complete factor H deficiency is associated with secondary severe depletion of circulating C3 together with reduction in the alternative pathway activation protein, factor B (Table 1). As a consequence of the reduced C3 levels, functional assays of complement haemolytic activity, whether triggered by alternative (AP50) or classical (CH50) pathway activation, are reduced or even absent.

Properdin levels are also usually reduced (cases 1a, 1b, 4a, 4b, 4c, 5, 8, 13, 14, two cases from family 9), although two factor H-deficient individuals from one family had normal values (cases 6a, 6b) as did two of the factor H-deficient individuals from family 9. Where reported, terminal pathway components are usually low. Thus, in the 17 factor H-deficient individuals in whom C5 levels were measured they were reduced in 14 (cases 2a, 2b, 3a, 3b, 3c, 4a, 4b, 4c, 5, 6a, 6b, 8, 9, 13, 14) and normal in only two individuals (cases 1a and 1b).

Plasma factor I levels remain normal in complete factor H deficiency. Notably, this is not the case in the converse situation. Thus, individuals with homozygous factor I deficiency develop secondary reduction in factor H, thought to be the result of binding of factor H to C3b [45].

The majority of factor H-deficient individuals have developed clinical disease, with only three individuals healthy at the time of reporting (cases 1b, 4b, 6b). As a consequence of secondary C3 deficiency there is a relatively high incidence of bacterial infection including *Neisserial* meningitis (cases 3a, 3b, 5, 8). However, the striking manifestation is that of renal disease. Renal disease has been reported in 28 of the 33 individuals that we have summarized in Table 1.

The renal manifestations include 15 cases of haemolytic uraemic syndrome (HUS, 1a, 6a, 9a–j, 10a, 10b, 15) and nine cases of membranoproliferative glomerulonephritis (MPGN, 3a, 3b, 3c, 11a, 11b, 2a, 2b, 12, 14). Furthermore, one individual was reported as type III collagen glomerulopathy (case 7) and another fibrillary glomerulopathy (case 13). A factor H-deficient individual with systemic lupus erythematosus (SLE) and lupus nephritis (case 4a) has also been reported, although it is important to note that this individual was also thought to have heterozygous C2 deficiency. Interestingly, one individual who presented with nephritic syndrome and renal biopsy showed MPGN type I [27]. However, this patient also had a history of hepatitis B infection, which is associated with MPGN type I independently of factor H dysfunction. Subsequently, the patient developed clinical features of HUS (progressive renal failure with thrombocytopenia and non-immune haemolytic anaemia), but no further renal biopsy was performed. Finally, we include one individual (case 4c) from the same family who was noted to have to have microscopic haematuria, although no renal biopsy was reported.

Clearly, factor H deficiency is associated with a markedly increased incidence of renal disease. However, an obvious question is why is this deficiency state associated with both MPGN and HUS? Before we attempt to answer this we will first define the renal histopathological features of both MPGN and HUS and secondly review the renal histopathological features reported in factor H-deficient individuals.

Renal histopathological features of MPGN and HUS

MPGN (also termed mesangiocapillary glomerulonephritis) refers to the morphological appearance of a glomerular lesion characterized by thickening of the glomerular capillary wall together with hypercellularity in mesangial areas, changes readily identified by light microscopy. As thus defined, the lesion is non-specific, occurring in a diverse range of conditions. These conditions have been placed into three categories, namely (i) associated with deposition of immunoglobulins and/or complement. This includes immune complex-associated MPGN type I, which may be primary or secondary (e.g. SLE, chronic infections including hepatitis C infection and subacute bacterial endocarditis); (ii) chronic thrombotic microangiopathies including late stages of acute HUS and thrombotic thrombocytopenia purpura; and (iii) paraprotein 'deposition' diseases which include type I cryoglobulinaemia, immunotactoid glomerulopathy and fibrillary glomerulopathy [46]. In the present context, this classification serves to emphasize the fact that the morphological appearance of MPGN can develop in chronic HUS. Distinguishing the underlying cause of MPGN

Table 1. Human factor H deficiency associated with very low or absent factor H levels.

Family	Onset, sex, race	Clinical features	Complement profile	Notes
1a [W] [38]	8 months, M, Asian (parents related)	Recurrent HUS Bilateral otitis media (*Haemophilus influenzae*) associated with HUS relapse Renal biopsy: HUS – see Table 2	CH50 13 μ/ml (25–45), AP50 4·5 μ/ml (12–26) C3 0·12 g/l (0·75–1·75) Factor B 35% (70–150), properdin 60% (60–130) C5, 6, 7, 8, 9 levels normal Factor I levels normal C3 nephritic factor absent	Free C3d in plasma using C3 crossed immuno-electrophoresis
1b [Z] [38]	3 years, M, Asian (parents related)	Healthy of	CH50 11 μ/ml (25–45), AP50 6 μ/ml (12–26) C3 0·17 g/l (0·75–1·75) Factor B 32% (70–150), properdin 60% (60–130) C5, 6, 7, 8, 9 levels normal Factor I levels normal C3 nephritic factor absent	Free C3d in plasma using C3 crossed immuno-electrophoresis
2a [case III-3] [23]	14 months, M, Algerian (parents related)	Recurrent macroscopic haematuria following infections from 14 months Renal biopsy: 'atypical DDD' – see Table 2	CH50 0% NHP, AP50 0% NHP C3 8% (70–150) Factor B 20% (65–150) C5 15% (60–150) C6 45% (60–140) C7 30% (60–110) C8 45% (60–140) C9 30% (70–150) Factor I levels normal C3 nephritic factor absent	Homozygous CYS431SER change affecting SCR7 [26]
2b [case III-5] [23]	4·5 months, M, Algerian (parents related)	Failure to thrive, macroscopic haematuria, otitis media (*Escherichia coli*) Recurrent pulmonary sepsis Renal biopsies: 'atypical DDD' – see Table 2	CH50 0%, AP50 0% C3 5% (70–150) Factor B 15% (65–150) C5 15% (60–150), C6 35% (60–140), C7 35% (60–110), C8 35% (60–140), C9 20% (70–150) Factor I levels normal C3 nephritic factor absent	Residual factor H present as evidenced by bright glomerular staining within mesangium and thickened glomerular capillary walls for factor H on IF studies of second renal biopsy
3a, b, c* [H1, H2, H3] [25]	3 female siblings	MPGN in all sepsis due to *Neisseria meningitidis* in two	CH50 < 5 μ/ml, AP50 < 10% in all C3 0·08, 0·12 and 0·07 g/l, respectively,* Factor B 15, 12 and 14% normal, respectively, C5 < 10% normal in all three cases C9 ≤ 10% normal Factor I levels normal – all cases C3 nephritic factor absent – all cases	Renal biopsy details not reported

4a [II-3] [37]	11 years, F, Italian (parents related)	SLE: psychosis, discoid skin lesions, chronic renal failure Skin biopsy (unaffected skin): positive lupus band test, i.e. IgM, IgA and C3 at dermo–epidermal junction Renal biopsy: lupus nephritis – see Table 2	CH50 absent C2 15% (75–120), C3 < 1 mg/dl (80–140) Factor B < 1 mg/dl (12–28) Properdin 47% (70–130) C5 5% (70–120), C6 52% (59–129), C7 38% (60–120), C8 21% (70–130), C9 35% (50–140) Factor I levels normal C3 nephritic factor absent	Heterozygous C2 deficiency Factor H and FHL-1 absent in sera [39] Homozygous GLU189stop change affecting SCR3 [39]
4b [II-4] [37]	?, M, Italian (parents related)	Healthy	CH50 absent C2111% (75–120), C3 < 1 mg/dl (80–140) Factor B < 1 mg/dl (12–28), Properdin 55% (70–130) C5 5% (70–120), C6 52% (59–129), C7 24% (60–120), C8 42% (70–130), C9 24% (50–140) Factor I levels normal C3 nephritic factor absent	Factor H and FHL-1 absent in sera [39] Homozygous GLU189stop change affecting SCR3 [39]
4c [II-2] [37]	?, F, Italian (parents related)	Asthma, haematuria	CH50 absent C2 44% (75–120), C3 < 1 mg/dl (80–140) Factor B < 1 mg/dl (12–28) Properdin 39% (70–130) C5 5% (70–120), C6 52% (59–129), C7 38% (60–120), C8 21% (70–130), C9 35% (50–140) Factor I levels normal C3 nephritic factor absent	Heterozygous C2 deficiency Factor H and FHL-1 absent on Western blotting [39] Homozygous GLU189stop change affecting SCR3 [39]
5 [36]	15 years, F, Danish	Two episodes of meningitis (*Neisseria meningitidis*)	CH50 < 2% NHP (> 67), AP50 < 38% (> 61) C3 < 2% NHP (> 84) Factor B 6% (>63), properdin 18% (> 70) C5 7% (> 68), C6 30% (> 63), C7 < 0·5% (> 61), C8 39% (> 75), C9 50% (> 53) Factor I levels normal C3 nephritic factor absent	Parents had 50% normal factor H levels C3dg and to lesser extent C3c elevated in plasma
6a [III-2] [35]	19 years, F, French-Canadian (parents unrelated)	3 episodes of HUS: the first was preceded by non-bloody diarrhoea, the second had no clear trigger and required dialysis for 9 months, the third was preceded by an upper respiratory tract infection renal biopsy: HUS – see Table 2	CH50 54% NHP (77–122), AP50 37% (75–125) C3 19 mg/dl (72–135) Factor B 17 mg/dl (22–48) Properdin 115% (82–119) C5 40% (67–133) C8100% (67–133) Factor I levels normal C3 nephritic factor absent	Female sibling died at early age from HUS

Table 1.

Family	Onset, age, sex, race	Clinical features	Complement profile	Notes
6b [III-3] [35]	24 years, F, French-Canadian (parents unrelated)	Healthy	CH50 51% NHP (77–122), AP50 38% (75–125) C3 19 mg/dl (72–135) Factor B 14 mg/dl (22–48) Properdin 92% (82–119) C5 50% (67–133) C8 75% (67–133) Factor I levels normal C3 nephritic factor absent	
7 [34]	6 years, M, Sioux n	14 months, recurrent haematuria and proteinuria	C3 < 27 mg/dl (88–155) Factor B 56 μg/ml (112–300)	FHL-1 present in sera
	Hypertension and heart failure at	Renal biopsy: Type III collagen glomerulopathy – see Table 2	Factor I levels normal	CYS536ARG affecting SCR9 on one allele, CYS959TYR affecting SCR16 on the other resulting in impaired FH secretion [40,41]
8 [II-9] [33]	59 years, F, Dutch, (parents unrelated)	Recurrent furunculosis in childhood, recurrent urinary tract infections, SCLE lesions on face from 30 years age, meninigitis aged 48 years (*N. meningitidis* serogroup X)	C3 absent using antigenic assay C3 haemolytic assay: 2–3% (75–125%) Factor B < 1% (13–22) Properdin 4·5–6 μg/ml (17–27·7) C2 9–13 U/l (18–23) C5 2–42% (76–136) C7 reduced Values represent ranges over 2 years C3 nephritic factor absent	FHL-1 present in sera Absent 37 and 42 kDa factor H-related proteins Reduced C2 levels also noted in some relatives hence possible heterozygous C2 deficiency
9a, b, c, d, e, f, g, h, i, j [32]	10 cases: 6 M and 4 F, median age at presentation 2 weeks (range 1–20 weeks) inbred Bedouin kindred from Southern Israel	All presented with HUS defined as acute renal insufficiency and microangiopathic haemolytic anaemia, three had diarrhoea – 10 patients died, one is alive on dialysis Renal biopsy: HUS – see Table 2	Full complement profile measured in 4 cases: C3 12, 0, 14, 0% (45–91) Factor B 18, 14, 57, 118% (36–86) Properdin 24, 54, 46, 90% (39–69) C5 34, 25, 52, 61% (41–103) C9 4, 18, 96, 89% (36–64) Factor I levels normal	Homozygous c.3747A > T transversion and 24 base in SCR20 resulting in deletion of the four most C-terminal amino acids [42,43] Normal factor H mRNA levels but defective secretion [44]
10a [patient 4] [31]	7 months, M, African	Hypertension, nephrotic syndrome, schistocytes on blood film Renal biopsy: HUS Long-term weekly FFP infusions maintained remission (Nathanson *et al.* 2001)	During remission: CH50 < 10% NHP (70–130) C3 < 3 mg/dl (65–110) Factor B < 12 mg/dl (16–40) Factor I levels normal C3 nephritic factor absent	FHL-1 present in sera Homozygous TYR899stop change affecting SCR15 [26]

10b [patient 5] [31]	11 months, M, African (first cousin of patient 10)	Haemolytic anaemia aged 1 month, HUS aged 11 months, now dialysis-dependent schistocytes on peripheral blood smear Renal biopsy: HUS	During remission: CH50 12% NHP (70–130) C3 < 3 mg/dl (65–110) Factor B < 12 mg/dl (16–40) Factor I levels normal C3 nephritic factor absent	150 kDa factor H protein absent on Western blotting but 42 kDa FHL-1 protein present Homozygous TYR899stop change affecting SCR15 [26]
11a [patient 3] [26]	?, M, Turkish brother of 11b	Presented with MPGN Clinical details unknown	C3170 mg/l (660–1250) Factor B 70 mg/l (90–320) CH50 < 10% (70–130)	Homozygous ARG127LEU change affecting SCR2 [26]
11b [patient 4] [26]	?, M, Turkish brother of 11a	Presented with MPGN Clinical details unknown	C3100 mg/l (660–1250) Factor B 50 mg/l (90–320) CH50 < 10% (70–130)	Homozygous ARG127LEU change affecting SCR2 [26]
12 [patient 6] [26]	8 years, F, Caucasian	Presented with nephritic syndrome MPGN type I	C3 < 40 mg/l (660–1250) Factor B 17 mg/l (90–320) CH50 < 10% (70–130)	Homozygous CYS673TYR change affecting SCR11 [26]
13 [29]	12 months, M, Turkish (parents related)	Periorbital oedema and microscopic haematuria aged 12 months No red cell fragments on blood film Renal biopsy: fibrillary glomerulopathy – see Table 2	CH50 < 10% (82–102) AP50 < 10% (84–150) C3 80 mg/l (825–1140) Factor B 44 mg/l (140–200) C5 97 mg/dl (120–160) Properdin 35% (80–120) Factor I levels normal C3 nephritic factor absent	
14 [patient 1] [27]	48 years, M	Nephrotic syndrome aged 48 years History of hepatitis B infection in childhood Renal biopsy MPGN type I – see Table 2 Subsequent relapse with clinical features of HUS (thrombocytopenia, anaemia and renal failure)	C3 < 0·10 g/l (0·67–1·29) Factor B 23% (59–154) Properdin 24% (54–157) C3d 32 mg/l (<7) C5 57% (72–171) Factor I levels normal	42 kDa FHL-1 protein present Homozygous PRO621THR change affecting SCR10
15 [30]	22 days, F, Korean	Generalized oedema, haematuria, proteinuria Renal failure, thrombocytopenia, schistocytes on peripheral blood smear Improved with FFP infusions, relapses frequently followed infections Renal biopsy: HUS – see Table 2	Persistently low C3	CYS1077TRP affecting SCR18 on one allele, GLN1139Stop affecting SCR19 on the other

( ) indicate normal ranges, first [] indicate case descriptors used in original reports, second [] denotes citation, %, % of standard, *ages, clinical details and normal ranges not reported. Mutation nomenclature: initiation methionine is amino acid number one, A of the ATG codon is nucleotide 74. AP50, alternative pathway haemolytic activity; CH50, total complement haemolytic activity; DDD, dense deposit disease; FFP, fresh frozen plasma; FHL, factor H-like protein; HUS, haemolytic uraemic syndrome; HUVEC, human umbilical vascular endothelial cells; NHP, normal human pool, MPGN, membranoproliferative glomerulonephritis; SCLE, subacute cutaneous lupus erythematosus; SCR, short consensus repeat.

requires ultrastructural assessment of the glomerulus using electron microscopy together with immunofluorescent studies assessing the presence of immunoglobulin and complement components.

In association with immune-complex diseases, MPGN is characterized typically by the presence of both complement and immunoglobulin within the glomerulus, together with the presence of subendothelial electron-dense deposits along the glomerular basement membrane (GBM). This subtype is referred to as MPGN type I.

Much less commonly, MPGN may be associated with the presence of glomerular C3 deposition in the *absence* of immunoglobulin. In this situation the electron microscopic appearance of the GBM commonly shows the characteristic changes described as dense deposit disease (DDD). The defining abnormality in DDD is the highly characteristic electron microscopic appearance of the GBM where there is striking transformation of the central part of the GBM (termed the lamina densa) by linear electron-dense material [47]. Electron-dense deposits may also be seen within the tubular basement membrane and mesangium. The light microscopic features of DDD include MPGN [48,49]. This latter observation led to the proposal that DDD should be considered a variant of MPGN [49], and DDD was referred to subsequently as MPGN type II. However, subsequent studies have emphasized the fact that MPGN is only one of the light microscopic features of DDD. For example, mesangial proliferative and necrotizing glomerulonephritis may be seen [50]. Moreover, in a recent study of 69 cases of DDD, an MPGN pattern was seen in only 17 (25%) of the biopsies [51]. The most common pattern was a mesangial proliferative lesion ($n = 30$, 45%). Crescentic ($n = 12$, 18%) and acute proliferative and exudative lesions ($n = 8$, 12%) were also noted. Irrespective of the glomerular morphology, DDD is associated with glomerular C3 deposition with little, if any, immunoglobulin [51]. In view of this, we do not think it is accurate to refer to DDD as a subtype of MPGN and hence will use the term 'DDD' in preference to 'MPGN type II' further in this review. The pathogenesis and therapy of DDD has recently been reviewed comprehensively [52].

A further subtype of idiopathic MPGN was described by Strife and colleagues [53]. In their report of seven individuals with MPGN they described GBM ultrastructural changes that were consistent with neither DDD nor MPGN type I. These biopsies demonstrated contiguous subepithelial and subendothelial deposits associated with basement membrane disruption. Granular deposition of C3 and properdin was present in these biopsies. Unlike DDD, immunoglobulins and Clq were variably present. This variant was termed MPGN type III.

HUS refers to the triad of renal failure, thrombocytopenia and non-immune microangiopathic haemolytic anaemia. The latter is demonstrated usually by the finding of red cell fragments (schistocytes) on peripheral blood smears. The acute renal lesion in HUS is thrombotic microangiopathy (TMA). Thrombotic microangiopathy may affect glomeruli, arterioles and arteries. In acute disease glomeruli show capillary loop thrombosis often with accumulation of fragmented red blood cells within capillary lumens. Ultrastructurally, there is damage to the endothelium with lifting of the endothelium from the basement membrane and the accumulation of flocculent material, sometimes containing fibrin and fragmented red blood cells, beneath the endothelium. Arterioles show thrombosis and fibrin, with their walls and arteries, may show marked loose myxoid expansion of the intima. With chronic injury the glomeruli develop laminated subendothelial thickening of the basement membrane.

In summary, the characteristic renal lesion associated with acute HUS is thrombotic microangiopathy. MPGN is a non-specific glomerular lesion. Clues to the aetiology of MPGN derive from a combination of immunofluorescence and ultrastructural studies. Hence, in DDD there is characteristic deposition of glomerular C3 without immunoglobulin together with electron-dense deposits within the central part of the GBM. In contrast, in MPGN associated with immune-complex disease, both immunoglobulin and C3 are present together with subendothelial electron-dense GBM deposits. An MPGN pattern associated with chronic thrombotic microangiopathy is associated with detachment of the endothelium from the GBM and the presence of sub-endothelial laminated thickening of the GBM without electron-dense deposits.

Renal biopsy findings in homozygous human factor H deficiency

We have summarized the reported renal biopsy findings in homozygous factor H-deficient humans in Table 2. In four reports of HUS and factor H deficiency renal biopsy findings were reported (Table 2). These biopsies showed convincing ultrastructural evidence of thrombotic microangiopathy, and included the presence of subendothelial deposits of flocculent material (cases 1a, 6a). Notably, there was no evidence of GBM electron-dense deposits and the clinical data indicated the presence of red cell fragments in all of these patients.

Conversely, in the cases reported by Levy *et al.* (cases 2a, b) the renal biopsies showed changes that had some features of DDD [23]. These included intramembranous electron-dense GBM changes together with glomerular C3 staining in the absence of immunoglobulin (case 2b). However, there were a number of pathological features that were not typical of DDD. First, electron-dense deposits were not seen in the basement membrane of Bowman's capsule or the tubular basement membranes which may be seen in DDD, albeit infrequently [51]. Secondly, deposits were also seen along the subendothelial part of the GBM (lamina rara interna, cases 2a and b). While subepithelial deposits have been noted in DDD in addition to the intramembranous change,

Table 2. Renal biopsy findings in individuals with human factor H deficiency associated with very low or absent factor H levels.

Case	Light microscopy	Immunofluorescence	Electron microscopy	Diagnosis
(a) Haemolytic uraemic syndrome				
1a [W] [38]	Diffuse mesangial and endothelial cell proliferation and swelling	n.a.	Capillary wall thickening due to subendothelial deposits of floccular material	HUS*
	Few capillary loops contained hyaline thrombi large vessels normal			
	Interstitium normal, tubules showed minor vacuolation only		Deposits of floccular material also seen in mesangium	
6a [III-2] [35]	Diffuse endothelial swelling with normal cellularity of glomerular tuft	Focal and segmental deposits of fibrinogen on glomerulus and afferent arteriole	Granular, fluffy and fibrillary subendothelial deposits with marked thickening of GBM	HUS*
	Necrotizing lesion affecting afferent arteriole	Discrete C3 deposits along capillary walls IgA, IgM,	Mild mesangial matrix expansion but no deposits	
	Tubulointerstitium normal	C1q, C3 deposits along afferent arteriolar walls		
9a–j	Four kidney biopsies from 3 patients and 2 autopsy specimens were studied and reported in summary form:			
[32]	Early stages of disease significant changes in arterioles and minor changes in glomeruli were noted	C3 staining noted on glomerular capillary walls while staining for IgG, IgA, IgM and fibrinogen was negative	Swollen endothelial cells narrowing lumen of interlobular arterioles	HUS*
	Arteriolar changes included: 'onion skin' changes, luminal stenosis and oedema, intimal thickening	Arteriolar walls stained intensely for actin		
	Glomerular changes included: endothelial swelling, mesangial proliferation and increased matrix formation. Very few capillary fibrin thrombi with platelet clumping were seen	Arteriolar walls stained intensely for actin		
	Second biopsy in patient 4, aged 6 months:			
	Advanced fibrotic change in glomeruli and tubulointerstitium			
15 [30]	Marked mesangial and endothelial cell proliferation and mesangial matrix with fibrillar appearance	Peripheral and mesangial staining for C3 and fibrinogen	Subendothelial widening and mesangial interposition without electron-dense deposit	HUS*
	Double-contoured glomerular capillary loops observed focally	No staining for type III collagen	Some fibrils in mesangium	
(b) Membranoproliferative glomerulonephritis				
2a [case III-3] [23]	Diffuse capillary wall thickening with double contours and	Abundant, bright granular deposits of	Diffuse, irregular thickening of the BM of the capillary loops and mesangial stalks due to presence of electron-dense, homogeneous argyrophilic deposits, located mainly within the internal part of the GBM	Atypical DDD
	Increased mesangial matrix	C3 in capillary walls and mesangial stalk		
	Arteries normal	Rare, segmental linear deposits were observed in the GBM		
	Interstitium normal			
	Few tubules showed thickened basement membranes	Deposits only contained C3		
		No deposits seen in tubular BM or within arteries	Mesangial interpositioning (mesangial cell cytoplasm in capillary walls) and focal effacement of foot processes	
			Mesangial matrix increased and contained electron-dense, homogeneous argyrophilic deposits	
			Interstitium normal	

Table 2.

Case	Light microscopy	Immunofluorescence	Electron microscopy	Diagnosis
2b	Biopsy one (aged 6 months):			
[case III-5]	Mesangial cell and matrix increase	Scattered, bright and granular C3 deposits in mesangial areas and diffuse linear C3 appearance in capillary walls	n.a.	Atypical DDD
[23]	Swollen endothelial cells			
	Frequent neutrophils and monocytes in capillary lumens			
	Occasional capillary wall double contours			
	Arteries contained swollen endothelial cells			
	Biopsy two (aged 2 years and 4 months):			
	Mesangial cell and matrix increase	Abundant, bright and granular C3 deposits in mesangial stalks and capillary walls	Irregular thickening of the BM of the capillary loops and mesangial stalks due to presence of electron-dense, homogeneous argyrophilic deposits, intramembranous in location with occasional enlargement of the lamina rara interna. Occasional effacement of foot processes	
	Swollen endothelial cells			
	Capillary walls diffusely thickened with occasional double contours	Few segmental linear C3 deposits along basement membranes		
	Epithelial cells hypertrophied			
	Moderate interstitial fibrosis	No C3 staining in tubular BM or arteries		
	Arteries contained swollen endothelial cells		Mesangial matrix increased and contained electron-dense, homogeneous argyrophilic deposits	
		C5b-9 present on mesangial stalks, thickened capillary walls and tubular BM	No deposits were seen in vascular, tubular or Bowman's capsule BM	
		Positive staining with rabbit anti-human factor H antibody detected on mesangial stalks and thickened capillary walls	Monocytes and neutrophils seen in capillary loops and between BM and endothelial cells	
14	MPGN with duplication of GBM	C3 deposits in capillary basement membrane and mesangium	Subendothelial GBM deposits	MPGN type I (see also text)
[patient 1]	Endothelial swelling and few thrombi noted in glomerular capillaries			
[27]	Global sclerosis in many glomeruli			
(c) Other				
7	Biopsy one (aged 13 months):			
[34]	Diffuse thickening of capillary loops with double contours	Trace mesangial and GBM staining for C3, C4, IgG, IgM, properdin and fibrinogen	Striking subendothelial widening by lucent granular and irregular membrane-like material	Type III collagen glomerulopathy (see also text)
	Glomerular endothelial proliferation and mesangial hypercellularity			
	Occasional arterioles with reduplication of elastic lamina		Mesangial interpositioning (mesangial cell cytoplasm in capillary walls)	
	Biopsy two (aged 2 years):			
	Diffuse thickening of capillary loops with double contours	Trace mesangial and GBM staining for C3, C4, IgG, IgM, properdin and fibrinogen	Subendothelial lucent space containing fibrillar material not organized into discrete deposits	
	Glomerular endothelial proliferation and mesangial hypercellularity			
	Occasional medial hypertrophy in afferent arterioles and interlobular arteries			
	Focal tubular atrophy			
	Biopsy three (aged 5 years):			
	Diffuse thickening of capillary loops with double contours	Trace mesangial staining for C1q, C4, IgG and IgM	Subendothelial and mesangial deposition of flocculent material not organized into discrete deposits	
	Glomerular endothelial proliferation and mesangial hypercellularity and increased matrix			
	Arteriosclerosis of all small vessels	Segmental C3 deposition in capillary loops	Mesangial interpositioning (mesangial cell cytoplasm in capillary walls) and hypercellularity	
	Focal tubular atrophy	Diffuse mesangial and capillary loop staining for type III collagen	Collagen fibrils in mesangium and capillary loops	