

MPGN II – genetically determined by defective complement regulation?

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Abstract MPGN II is a rare disease which is characterized by complement containing deposits within the GBM. The disease is characterized by functional impairment of the GBM causing progressive loss of renal function eventually resulting in end stage renal disease.

It now becomes evident that in addition to C3NeF, which inhibits the inactivation of the alternative C3 convertase C3bBb, different genetically determined factors are also involved in the pathogenesis of MPGN II. These factors though different from C3NeF also result in defective complement regulation acting either through separate pathways or synergistically with C3NeF. Following the finding of MPGN II in Factor H deficient animals, patients with MPGN II were identified presenting with an activated complement system caused by Factor H deficiency. Factor

H gene mutations result in a lack of plasma Factor H or in a functional defect of Factor H protein. Loss of Factor H function can also be caused by inactivating Factor H autoantibodies, C3 mutations preventing interaction between C3 and Factor H, or autoantibodies against C3.

Identification of patients with MPGN II caused by defective complement control may allow treatment by replacement of the missing factor via plasma infusion, thus possibly preventing or at least delaying disease progress.

Keywords Membranoproliferative glomerulonephritis type II (MPGN II) · Alternative pathway of the complement system · C3 nephritic factor (C3NeF) · Factor H · Factor H autoantibodies

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Introduction

Membranoproliferative glomerulonephritis type II (MPGN II) or “dense deposit disease (DDD)” is a rare disease which is characterized by complement (e.g. C3) containing dense deposits within the basement membrane of the glomerular capillary wall, followed by capillary wall thickening, mesangial cell proliferation, and glomerular fibrosis (Fig. 1) [1, 2]. In some patients extrarenal manifestations like lipodystrophy and retinal alterations, e.g. soft drusen or age-related macular degeneration (AMD) caused by complement deposits within Bruch's membrane can be found [1, 3].

Besides MPGN II two different subtypes, MPGN I and MPGN III, are known. These subtypes are also characterized by mesangial cell proliferation and increased mesangial matrix combined with thickening of the glomerular capillary wall, but—different from MPGN II—MPGN I and III are considered immune complex-mediated diseases.

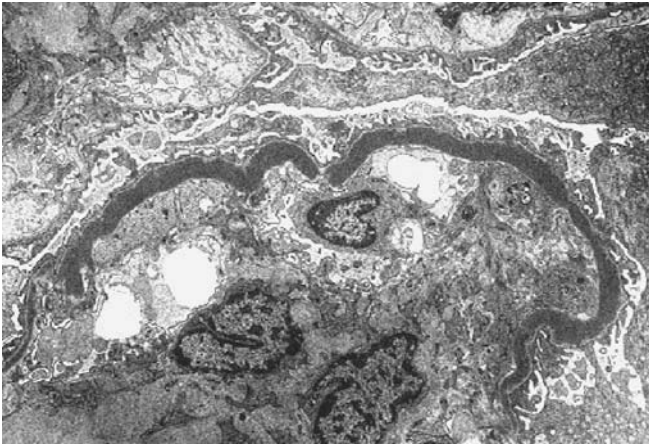


Fig. 1 Electron microscopy of renal biopsy specimen of membranoproliferative glomerulonephritis II (MPGN II): Typical findings of MPGN II with thickening of the glomerular basement membrane (GBM) caused by deposits within the lamina densa (“dense deposit disease”)

Deposits in all MPGN subtypes contain C3 and other complement factors [2, 4].

Information about the prevalence of MPGN is rare and differs depending on age and region: while in adults MPGN is considered to be one of the major causes of nephrotic syndrome with 0.2–20% of all primary glomerulopathies (Europe and North America) [5], the frequency in children is 6.2% [6]. In Asia, South America and Africa MPGN accounts for 30–40% of all cases of nephrotic syndrome [5].

MPGN mainly affects older children and adolescents (median age at onset of disease is about 10 years). Half of the patients present with nephrotic syndrome, the others with mild proteinuria, 20% with macrohematuria. About one third develops hypertension at onset of disease. Children with MPGN have an unfavourable prognosis and develop end stage renal disease (ESRD) during late childhood or early adolescence [2, 7, 8].

The recent observation that animals lacking plasma Factor H, the main soluble regulator of the alternative complement pathway, develop MPGN II further supports the notion that the complement system is involved in the pathogenesis of MPGN II, and that defective complement control is a major cause for this disease [9–11]. This concept is supported by the presence of C3 nephritic factor (C3NeF)—an IgG autoantibody which stabilizes the alternative C3 convertase C3bBb, thus preventing degradation of this complex—in some MPGN II patients [12–14]. Even though C3NeF not only shows inter- but also intra-individual variability, the presence of this factor suggests a crucial role of complement dysregulation in the pathogenesis of MPGN II. Both the presence of C3NeF and the absence or defective function of Factor H result in unrestricted activity of the alternative C3 convertase

C3bBb leading to complement activation and deposition of activated complement components within the glomerular basement membrane (GBM).

Alternative pathway of the complement system: central role of Factor H

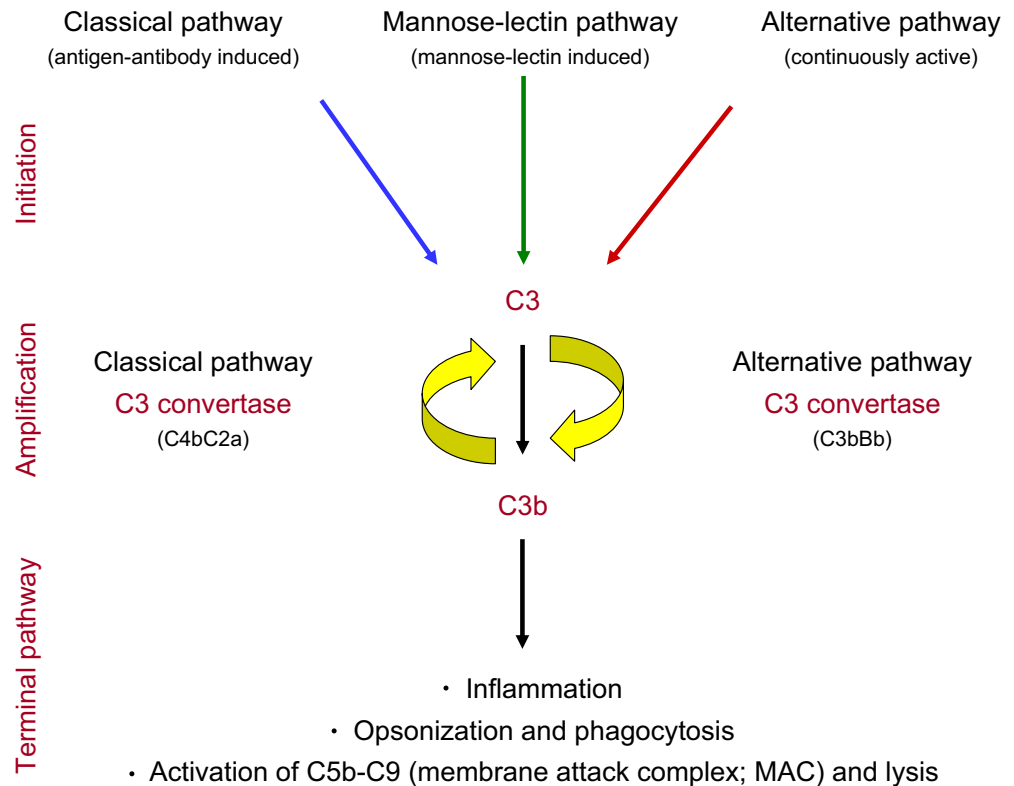
The complement system belongs to innate immunity and is mainly designed to defend the body against invading microbes such as pyogenic bacteria or fungi. Complement can be activated by three different pathways. While the classical and lectin pathways are initiated by antigen-antibody complexes (classical pathway) or repetitive carbohydrate structures (mannose lectin pathway), the alternative pathway is constantly active and therefore needs to be tightly regulated by inhibition in order to avoid fatal self attack of the body [3, 15–18].

The central complement protein C3 is spontaneously activated by constant low rate cleavage (C3 “tick over”) which results in the generation of a conformationally altered C3, termed C3(H₂O) which, upon binding to and activation of Factor B, cleaves additional C3 molecules (initiation phase). The newly generated C3b may bind to cell surfaces and, together with other soluble factors, form the surface bound alternative pathway C3 convertase, C3bBb, which is further stabilized by properdin. On an activator surface this enzyme rapidly activates and binds more C3 molecules and accelerates activation (amplification loop). If not limited at this stage, the complement cascade proceeds unrestrictedly until the terminal complement complex (TCC) is formed and the actions of the complement cascade (e.g. opsonization and phagocytosis of cells, lysis of cells, inflammation) are carried out (Fig. 2). Different from invading microbes which lack such regulators, host cells—with few exceptions—are protected by a redundant system of soluble and membrane anchored factors¹ which ensure that complement activation exclusively occurs site and time-restricted [3, 15–18].

Among these complement regulators, plasma Factor H is of significant importance to the homeostasis of the alternative pathway. Factor H competes with Factor B for binding to C3b-targeted surfaces by mechanisms which are not entirely understood [19, 20]. Obviously, surface charge and the content of sialic acid support Factor H binding. Furthermore, Factor H destabilizes C3bBb (decay accelerating activity) and—as cofactor of Factor I—inactivates

¹ Soluble: C1 inhibitor, C4 binding protein, Factor H and FHL-1 (Factor H like protein=alternate splice variant of Factor H); FHR-1 (Factor H related protein-1), Factor I, clusterin, vitronectin (S-protein) Membrane anchored: MCP (membrane cofactor protein); DAF (decay accelerating factor); CR1 (complement receptor 1)

Fig. 2 The crucial role of the alternative pathway C3 convertase C3bBb within the activation cascade of the complement system



C3b (cofactor activity). Control of C3bBb activity within the activation cascade of the complement system is the key to complement control and, vice versa, unrestricted C3bBb activity results in severe inflammation (Fig. 2) [3, 15–18].

MPGN II due to missing Factor H activity

MPGN II is caused by at least three different scenarios which are listed here in order of frequency [21]:

1. C3 nephritic factor (C3NeF)
2. Missing or impaired Factor H activity
 - (a) Factor H deficiency
 - (b) Factor H defect
 - (c) Blocking/inhibitory Factor H autoantibodies
3. Rare causes
 - (a) Mutant Factor H binding site of C3 (Marder's disease)
 - (b) C3 autoantibodies

In addition to MPGN II other diseases like atypical hemolytic uremic syndrome (aHUS) and recently also adult macula degeneration (AMD) have been linked to defects in complement regulation, namely, to the Factor H protein family [3]. However, until today it remains unclear why not all patients with Factor H deficiency develop MPGN II but can also develop aHUS [22, 23].

C3 nephritic factor (C3NeF)

It is well known that the IgG autoantibody C3NeF is linked to MPGN II [12]; about 55% of the adult and 80% of the pediatric MPGN II patients are positive for C3NeF [24]. However, C3NeF is not only observed in patients with MPGN II but also in patients with MPGN I and MPGN III², partial lipodystrophy, retina alterations, meningococcal meningitis and even in healthy individuals [3]. Moreover it is possible that the same patient is first tested C3NeF positive but becomes negative during the course of disease (or vice versa) [24].

Both C3NeF and Factor H control the same “enzyme”, the alternative pathway C3 convertase C3bBb. Factor H dissociates the C3bBb complex (decay accelerating activity) and, together with Factor I, inactivates C3b (cofactor activity) and prevents further binding of Factor B. However, C3NeF displays the opposite effects: C3NeF stabilizes the convertase and increases the half life of this “enzyme” approximately 10-fold [25, 26]. Thus, the presence of C3NeF, absence or defective function of Factor H, and inhibition of Factor H function by antibodies via different mechanisms cause lack of C3bBb control which finally results in unrestricted complement activation.

² Distribution of C3NeF in serum depending on different histological types of MPGN: MPGN II > MPGN I > MPGN III [24].

Missing or impaired Factor H activity

Factor H deficiency

Absence of Factor H in plasma as a cause of MPGN II has been observed in humans, in naturally mutant Factor H deficient pigs, and in genetically engineered Factor H knock out mice [3].

Analysis of the genetic defects leading to complete deficiency of Factor H in plasma of patients revealed homozygous or compound heterozygous Factor H gene mutations in SCRs³ 2, 4, 9, 11, and 16 which result in non-framework amino acid exchanges or in mutations of framework Cys residues affecting disulphide bond formation within the Factor H molecule [28, 29].

Factor H deficient pigs represent natural mutants [9, 10], and Factor H knock out mice were genetically designed [11]. Deficient pigs display amino acid mutations located within SCRs 9 and 20 [30].

All these mutations result in a block of protein secretion: the mutant protein is expressed in hepatocytes, but is retained in the endoplasmic reticulum, thereby accumulating in the cytoplasm. In consequence, absence of Factor H in plasma causes sustained activation of the alternative complement pathway reflected by consumption of C3 and accumulation of the C3 degradation product C3d in plasma [3, 30].

Factor H defect

Different from the absence of Factor H in plasma we recently described a novel pathomechanism for MPGN II: two siblings with MPGN II and complement activation expressed normal plasma levels of a mutant, functionally defective Factor H protein and, in addition, were both positive for C3NeF. Genetic analysis revealed several mutations within the Factor H gene. One—considered relevant for disease—causes deletion of three nucleotides (genomic DNA: 57967–57969; cDNA: 743–745) and results in homozygous deletion of a Lys residue in position 224 (K₂₂₄) located within the complement regulatory domain of Factor H protein in SCR 4. Functional studies of the mutant Factor H protein isolated from the patients revealed normal C-terminal activity—binding to heparin, cell surfaces and C3d—while N-terminal functions, cofactor and decay accelerating activity, as well as binding to the central complement component C3b, were severely reduced. Both parents carried the mutation heterozygously

³ Factor H consists of 20 short consensus repeats (SCR) or complement cofactor proteins (CCP). N-terminal SCRs 1–4 form the regulatory domain of Factor H (cofactor and decay accelerating activity, binding to C3b), C-terminal SCRs 19+20 form the recognition domain (heparin and cell binding, binding to C3d) [27].

but normal Factor H function was observed in plasma, and the complement system was not activated.

Both patients in addition their healthy mother were positive for C3NeF indicating that defective control of the alternative pathway by both C3NeF and Factor H dysfunction supports the development of MPGN II in the two patients whereas in this study C3NeF alone in the absence of mutant and functionally defective Factor H did not per se cause disease in the mother [31].

Blocking/inhibitory Factor H autoantibodies

Meri et al. isolated a factor associated with dysfunction of the alternative complement pathway from serum and urine of a patient with hypocomplementemic MPGN II (atypical histology with additional subendothelial deposits: intermediate type between MPGN I and II). When mixed with fresh normal serum the patient's serum induced almost complete conversion of C3. This activity was due to a circulating factor different from C3NeF but was observed to interact directly with Factor H and can therefore be considered as Factor H autoantibody. The binding site of the antibody was localized to SCR 3 within the regulatory domain of Factor H which explains impairment of the complement regulatory function of Factor H [32, 33].

Rare causes

Mutant factor H binding site of C3 (Marder's disease)

Marder et al. described a mutation in C3 which alters the Factor H binding site. This mutation renders the C3b molecule unable to bind Factor H, thus preventing Factor H mediated dissociation of the alternative pathway convertase C3bBb. In consequence, this defect, called Marder's disease, which was so far found only in a very small group of patients, also prevents control of C3bBb activity and thereby causes unrestricted complement activation [34, 35].

C3 autoantibodies

Normal human IgG contains naturally occurring anti-C3 antibodies (anti-C3 NABs) that have been proposed to regulate complement amplification. Anti-C3 NAB preparations exhibited nephritic factor activity that was up to 60 times stronger than that of total IgG from a patient with MPGN II. Anti-C3 NABs associated with framework-specific anti-idiotypic NABs stabilize C3 convertase and promote its generation but their activity is compensated for in whole IgG [36].

A redundant system composed of soluble and membrane anchored regulators normally prevents unrestricted complement activation on host cells. Certain tissue surfaces,

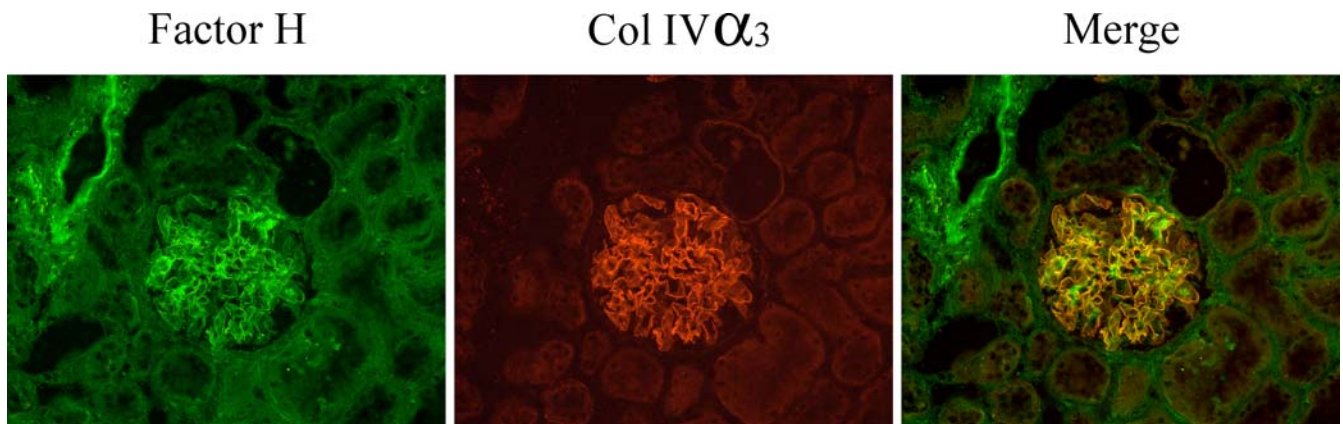


Fig. 3 Light microscopic immunofluorescence double labeling of Factor H (green fluorescence) and collagen type IV α 3 (red fluorescence) in a normal human kidney specimen; co-localization in glomeruli is indicated by yellow fluorescence (merge). For indirect immunofluorescence, cryostat-cut sections were fixed in cold acetone, blocked with 10% normal goat serum, and incubated in primary antibodies

overnight at 4°C using a rabbit polyclonal antibody against Factor H (N-terminal domain; dilution 1:500) and a rat monoclonal antibody against collagen type I α 3 (dilution 1:5; gift of Dr. Y. Sado, Kumamoto, Japan). Antibody binding was detected by Alexa 488- and Alexa 555-conjugated secondary antibodies (Molecular Probes)

however, lack membrane anchored regulators. Consequently these structures exclusively depend on attached soluble regulators like Factor H. The GBM represents such a sensitive structure [3, 21]. Supporting the important role of Factor H for protection of the GBM, Factor H colocalizes with collagen IV α 3 (COLIV α 3) (Fig. 3). In addition, a transmembrane gradient of Factor H across the GBM is found with maximum Factor H concentration on the blood and minimum Factor H concentration on the urine side of the GBM (Fig. 4).

Lack or inactivity of Factor H results in continuous C3 deposition within the “lamina densa” of the GBM which is the layer in which under physiological conditions Factor H

is detected in the highest concentration (Fig. 4). This results in thickening of the GBM and DDD with subsequent impairment of the glomerular filter function, hematuria and proteinuria, and eventually loss of renal function.

Therapeutic perspectives

So far there is no standard treatment for MPGN II. Individual treatment concepts include the use of steroids (prednisone), alkylating substances (cyclophosphamide) or other immunosuppressive agents (e.g. mycophenolate mofetil), anti inflammatory and anti platelet aggregating agents

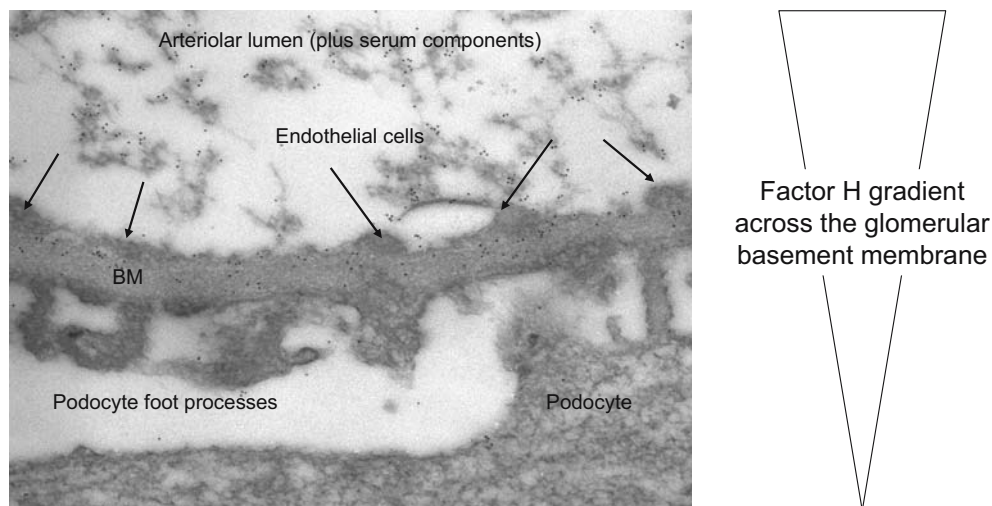
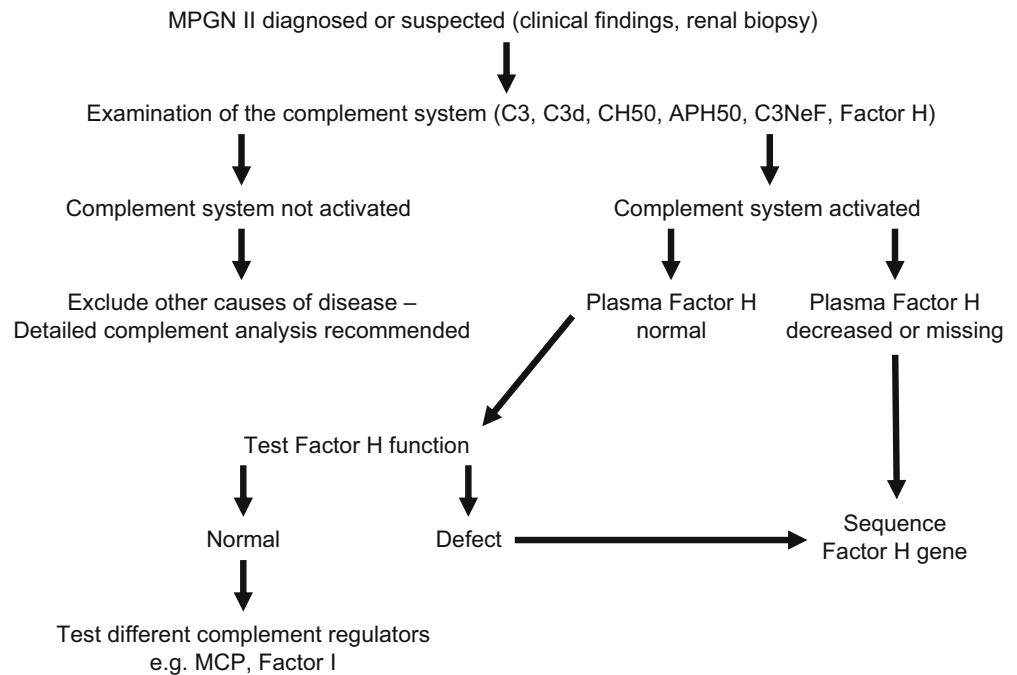


Fig. 4 Electron microscopic immunogold localization of Factor H along the glomerular basement membrane (GBM) of a normal human kidney specimen revealing a transmembrane gradient of Factor H across the GBM with maximum Factor H concentration on the blood side and minimum Factor H concentration on the urine side of the GBM. For postembedding immunogold labeling, tissue specimen were fixed in 4%

paraformaldehyde and 0.1% glutaraldehyde in 0.1 M cacodylate buffer for 5 hr at 4°C and embedded in resin (LR White). Ultrathin sections were blocked with 0.5% ovalbumin and 0.5% fish gelatin, incubated in primary antibody (Factor H, N-terminal domain; dilution 1:200) overnight at 4°C and in 10 nm gold-conjugated secondary antibody (BioCell) for 1 hr, followed by staining with uranyl acetate

Fig. 5 Diagnostic algorithm for diseases caused by defective complement regulation



(e.g. dipyridamole, acetylsalicylic acid, dicumarol) as monotherapy or in various combinations and treatment of possible concomitant diseases like hypertension (e.g. diuretics, ACE inhibitors, AT-1 antagonists) [37, 38]. Angiotensin converting enzyme (ACE) and/or angiotensin II subtype 1 (AT-1) receptor inhibitors can be used to reduce proteinuria and to protect the kidney against the development of tubulointerstitial fibrosis (TIF) [39, 40].

With the concept presented here of complement based pathogenesis of MPGN II, however, replacement of missing or functionally defective complement factors which lead to unrestricted complement activation becomes a possible therapeutic option, and periodical plasma infusions seem to represent an adequate regimen [1, 29]. This concept is supported by the beneficial effect of the infusion of porcine plasma to piglets with MPGN II caused by Factor H deficiency [9, 30], and by results recently obtained in a mouse model of chronic serum sickness indicating a disease limiting effect of Factor H substitution [31, 41].

With respect to recent experiences in the treatment of complement based aHUS, plasma volumes of 10–20 ml/kg/treatment and intervals of 14 days seem to be adequate and, based on a Factor H half life of about 6 days, may be a reasonable approach in MPGN II patients with comparable Factor H deficiencies [23].

Pure Factor H—either isolated from plasma or in recombinant form—may become a therapeutic instrument for the future. The use of this agent could help to reduce the risk of contamination and would simplify the treatment of patients by allowing subcutaneous or intramuscular application as compared to the current routine of outpatient clinic visits, e.g. every 14 days for plasma infusions.

Besides replacement of deficient or defective complement regulators, plasmapheresis might be a therapeutic option for patients in whom MPGN II is caused by the presence of C3NeF or different Factor H inactivating antibodies. In support of this approach, Kurtz et al. reported a child with rapidly progressive recurrent MPGN II at the background of the presence of C3NeF. In this patient disease progression towards onset of chronic renal failure was delayed by periodic plasmapheresis [42].

In consequence of this “extended concept” of MPGN II as a disease which may also be genetically determined by defective complement regulation and encouraged by the continuously growing insights into the details of the underlying mechanisms we suggest a “diagnostic algorithm” to systematically identify the disease causing complement defect in an individual patient (Fig. 5). The earlier the potential defect is identified the sooner replacement therapy by plasma infusion can be induced which might prevent or at least delay disease progression.

It is without question that the “extended concept” of complement activation presented here as a cause of MPGN II needs to be further evaluated. For this purpose we established a registry (<http://www.mpgn-registry.de>) as an instrument to examine frequency and course as well as underlying pathogenetic principles of this rare disease.

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