GLOMERULONEPHRITIS ASSOCIATED WITH DEFICIENCIES AND POLYMORPHISMS OF COMPLEMENT COMPONENTS ENCODED IN THE CLASS III REGION OF THE MHC

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1. ABSTRACT

An association between the complement system and immune complex glomerular disease in humans has long been recognized. In fact, much of our early understanding of the immunochemistry of complement activation developed with the study of acute and chronic glomerulonephritis (1). This manuscript will examine associations between glomerulonephritis and the three complement components encoded within the major histocompatibility complex: C4, C2, and factor B (B). The mechanisms by which deficiencies or polymorphisms in these components can mediate disease will be examined.

2. INTRODUCTION

The complement system is germane to glomerulonephritis in two distinct ways. Most often discussed is the role of complement activation as an *effector mechanism*. Immune complexes, either trapped in the glomerulus or formed *in situ*, activate complement, causing direct tissue injury and recruiting other inflammatory mediators (2). Evidence for this mechanism includes deposition of complement components in areas of tissue injury (3), decreased plasma concentration of components (4), and the presence of circulating activation products (5). Most of the data supporting this process come from studies of acute glomerulonephritis. Data that are more recent have also suggested a role for locally synthesized complement in progressive renal injury associated with chronic glomerulonephritis (6).

In addition to an effector role, there is also much evidence that *deficiencies or polymorphisms* of specific components can result in an increased susceptibility to glomerulonephritis. Although this association has been suggested for a variety of components, most study has centered on the three (C4, C2, and B) which are encoded within the MHC on the short arm of chromosome 6. This paper will review the major glomerular processes for which this association has been made.

3. COMPLEMENT C4

The genetics of C4, as reviewed elsewhere in this symposium, are the most complex of that of any complement component. Similarly, the associations between glomerular disease and inherited abnormalities of the component are extensive.

3.1. Complete deficiency

With virtually no exception, well-documented complete deficiency of C4 (ie. complete deficiency of both the C4A and C4B isotypes) is associated with autoimmune disease (7). In most cases, these individuals are homozygous for an unexpressed C4A gene and a C4B gene deletion (8). In some situations, this is associated with consanguinity (9), but at least one (10) uniparental disomy has been shown.

The typical extrarenal features of the autoimmune disorder in these patients include the presence of

autoantibodies, especially anti Ro and anti La, as well as a prominence of cutaneous disease (11).

Varieties of renal manifestations have been seen with this deficiency. One of the earliest reports was that of a Henoch-Schönlein purpura–like lesion. This individual had cutaneous and gastrointestinal vasculitis, as well as a progressive glomerulonephritis, and apparently did not have any autoantibodies (12). He developed renal failure, and had recurrence of disease in a transplanted kidney.

This case is very difficult to interpret in the context of other reports. The clinical, serologic, and pathologic findings in this individual differ from those in other reported patients. The patient has many features in common with those seen in cryoglobulinemic states (13). Acquired reductions in plasma C4 concentration, often to barely detectable levels, occasionally accompany cryoglobulinemia.

In the other reported cases, clinical renal involvement has ranged from absent (14) to a severe nephrotic syndrome (15). Corresponding renal histopathology has ranged from mild mesangial expansion (16) to severe diffuse proliferative glomerulonephritis (10,15). Immunohistology, where available, has shown evidence of IgG and C3 deposits in the glomeruli, with complement activation presumably occurring via the alternative pathway. There are few reports providing data on the plasma concentrations of other complement components in such individuals. The patient reported by us (10), however, has had multiple determinations of plasma C3 concentration, all of which have been normal. Some other reported patients have also had normal C3 levels. One interpretation of this observation would be that alternative-pathway mediated renal injury and classical-pathway-mediated hypocomplementemia can be independent events in SLE. The one reported patient who had a reduction in plasma C3 (15) had a co-existing nephrotic syndrome, a sufficient explanation in and of itself for mild hypocomplementemia (17).

Progression of glomerular injury to renal failure necessitating transplantation has been reported at least once. This however, was in the patient described above whose course was somewhat unusual (12).

Death has occurred in some of these patients, although apparently not directly from their renal disease. Rather, infection appears to be the cause of death in most reported patients, including another unreported child from our institution who developed Pneumocystis pneumoniae infection following treatment of glomerulonephritis with cyclophosphamide. This observation, as well as the often-mild course of renal disease in C4 deficient patients, has led us to avoidance of immunosuppressive therapy. In a single case, this resulted in an apparently successful use of intravenous immunoglobulin (18).

3.2. C4A isotype deficiency

In a seminal study, Fielder and coworkers reported an association between deficiency of the C4A isotype and SLE (19). These workers suggested that complement dysfunction consequent to the isotype deficiency resulted in the observed disease susceptibility. Since this original report, there has been a proliferation of studies, which have expanded upon this observation, and have suggested mechanisms for it.

Most chromosomes containing a deleted C4A gene include the MHC extended haplotype HLA A-1, B-8, DR3, SCO1 (20). This haplotype, which comprises about up to 10% of MHC haplotypes in Caucasians of North European heritage, is independently linked to a variety of autoimmune disorders and immunodeficiencies (21). In addition to SLE (22), the haplotype is over-represented in patients with disorders such as membranoproliferative glomerulonephritis (23), membranous glomerulopathy (24), diabetes mellitus (25), and celiac disease (26).

The concept of the extended haplotype implies uniformity of the genes within the haplotype (20). Excluding the HLA and complement genes, there are several distinct genes within this complex in humans (27). Which gene(s) is the proximate cause of immune disease susceptibility has not been established. It is unlikely, however, that the C4A deficiency per se the important factor. The majority of individuals in whom autoimmune diseases are associated with the haplotype are heterozygotes. Given the wide variation in normal human C4 plasma concentrations, it seems implausible that minor alterations in the levels of a single isotype could translate into important physiologic disruptions. Thus, in SLE and similar disorders, heterozygous C4A deficiency is most likely merely a marker for the presence of a haplotype on which some other disease susceptibility gene resides.

In contrast, complete homozygous phenotypic C4A deficiency appears to be a risk factor for SLE well beyond that which would be predicted by the presence of the common C4A deletion-containing extended haplotype. Complete C4A deficiency occurs in about 14-20% of Caucasians with SLE, as compared to about 1-2% of normals; the relative risk for SLE with homozygous C4A deficiency is about 8 (22).

Also supporting a primary role for complete isotype deficiency in SLE high is the clinical similarity of patients sharing this trait. A recent multicenter report of 18 patients with SLE and complete C4A deficiency (28) showed that they shared a variety of features, including paucity of renal disease and a tendency to have milder clinical manifestations. The generally good outcome of these patients is particularly important to keep in mind while following them. Since individuals with two unexpressed C4 genes may have low plasma concentration of C4 (29), care must be taken not to base inappropriately aggressive immunosuppressive therapy on the presence of a low C4 concentration alone.

3.3. C4B isotype deficiency

In contrast to the situation with C4A, C4B deficiency haplotypes display a wide variety of abnormalities, including C4A duplication, C4B deletions, and unexpressed genes (30). Although some C4B deficiency genes are associated with specific MHC extended haplotypes, most occur randomly. Thus, individuals with complete C4B deficiency generally display a variety of MHC haplotypes.

The principle glomerular lesion associated with complete C4B deficiency is IgA nephropathy. This observation was originally made by McLean *et al* (31). These workers actually reported an association between any C4 isotype deficiency and nephropathy. Examining their data, however, it is clear that C4B deficiency is the only important association. Their patients included only a single C4A deficient patient with IgA nephropathy, not significantly more than would be expected in a similar size group of Caucasians. Thus, their data made an even more compelling case for a specific association between C4B deficiency and IgA nephropathy.

The importance of C4B deficiency in this disorder was further established by studies from our group (32). In contrast, efforts at establishing a complete MHC haplotype association for this disease, as has been done for SLE, have been unsuccessful. The phenotype of complete C4B deficiency by itself seems well established as an independent risk factor for this glomerulopathy. Henoch-Schonlein purpura (HSP) may be considered a systemic form of IgA nephropathy, with cutaneous, serosal, and periarticular involvement accompanying an identical glomerular lesion. Not unexpectedly, an association between HSP and C4B deficiency has also been suggested (31, 33). Data on this association, however, are less consistent than those related to primary IgA nephropathy. Interestingly, some studies of IgA related renal diseases and HLA antigens show a slight preponderance of HLA DR4 (34). Some DR-4 containing haplotypes are extended haplotypes containing C4B null genes.

The explanation for the association between C4B deficiency and IgA nephropathy is no more understood than that of the C4A deficiency SLE association. There is a little evidence, for example, that C4 plays an important pathophysiologic role in IgA nephropathy. The protein is never found as a component of glomerular immune deposits, and reduction in plasma C4 concentration is not usually a feature of the disease. At a more basic level, there is also no compelling evidence that the classical pathway of complement is involved in the handling of IgA containing immune complexes.

One potential mechanism for this association relates to susceptibility to infection. Exacerbations of IgA nephropathy are frequently associated with acute febrile infections. If the complement isotype deficiency were to increase susceptibility to such infections, it might correspondingly lead to symptomatic disease. Data to support this hypothesis, however, are scant. While we (35) have found an increased susceptibility to bacteremia with encapsulated bacteria in children with C4B deficiency, others (36) have not confirmed this. In any case, these infections are not the most likely to trigger exacerbations of the glomerulopathy. This is clearly an area in which additional study is needed.

3.4. Other C4 polymorphisms

Although the C4 genes are extraordinarily polymorphic, there are no consistent reports of the polymorphisms being associated with kidney disease outside of extended haplotypes or complete isotype deficiency.

A single report in 1984 suggested that an allotype the investigators called "C4B2.9" was strongly associated with membranoproliferative glomerulonephritis (37). In an extensive study of this disease, however, we were unable to confirm this observation. We later concluded that the "C4B2.9" in the previous report was actually an acquired electrophoretic variant, associated with uremia from any cause (38). Thus, this "allotype" is neither a genetic C4 variant nor a specific marker of any glomerulopathy.

4. FACTOR B

In comparison to C4, the polymorphism of factor B is much less extensive. At the protein level, there are only three or four common allotypes of this component.

4.1. Complete deficiency

Factor B is one of the few complement components for which deficiency has never been described (39). B levels may be reduced in conditions associated with ongoing alternative pathway activation. At times, these serum levels may be reduced enough to suggest heterogeneous deficiency of the protein.

At least one of these conditions, Marder disease, has an autosomal dominant inheritance (40). The actual genetic defect appears to be in C3; patients appear to have an abnormality of H binding to the alternative pathway C3 convertase, resulting in unregulated consumption of C3 and B. Although some of these individuals have glomerulonephritis, other affected family members may be phenotypically normal. This condition, rather than an abnormality of B, should be suspected in any situation in which an inherited pattern of reduction in serum B concentration is found.

4.2. Factor B Polymorphism

There are no consistent reports of functional differences between the allotypes of B. Similarly, direct associations between B polymorphisms and specific glomerulonephritides are rarely described. There are, however, two studies dealing specifically with B polymorphism and glomerular disease.

In 1987, a German group examined B allotypes in 67 patients with IgA nephropathy. The BfF allele was marginally increased in frequency in the population (.33 vs .2 in controls). More significantly, the phenotype of BfFF occurred in none of the controls but 10.4% of the IgA nephropathy patients (41). Apparently, this study has not been replicated.

In a Japanese study reported in 1988, polyacrylamide gel isoelectric focusing was used to subtype the BfF allele. The BfFB suballele was a significant (P<0.001) risk factor for idiopathic membranous nephropathy (42). This study, as well, has not been replicated.

With these exceptions, the only studies addressing the association between B polymorphisms and glomerular disease have been in the context of one MHC extended haplotype HLA A1, B8, DR3, SCO1. Thus, the association between the BfS allele and both SLE and membranoproliferative glomerulonephritis completely derives from a primary association with this extended haplotype (22, 23).

5. COMPLEMENT C2

As is the case with B, the polymorphism of C2 is much less extensive and complex then that of C4 (43). On the other hand, deficiency of C2 is the most common component deficiency in the complement system (4).

5.1. Complete deficiency

Most reported patients with C2 deficiency carry the extended haplotype HLA A25, B18, DR2, SO42. On this haplotype, the C2 gene contains a 28 base pair deletion which results in a transcript with a deletion of exon 6 and a premature stop codon (44). A few (about 10%) C2 null genes occur on other haplotypes. C2 deficiency, unlike that of C4, is not uniformly associated with disease. The abnormality has been identified in normal individuals and in patients undergoing immunodeficiency investigation for a variety of recurrent infections (39). Unlike the situation with terminal component deficiencies or that of C3, the specific type of infection seems to be less uniform with C2 deficiency.

There does appear to be an increased susceptibility to SLE among individuals with complete C2 deficiency, although this finding is not nearly as uniform as the situation with C4. Furthermore, the spectrum of disease severity in C2 deficiency-associated SLE does not appear to vary from that seen in C2 replete patients.

There is a paucity of published studies of the glomerular lesions in C2-deficiency associated SLE. A well-characterized patient reported in 1994 had a history of recurrent bacterial infection and developed an illness initially characterized as acute rheumatic fever. Within a few weeks, this had evolved into typical SLE. She had a minimal nephritis classified as WHO Class II by biopsy (45).

There are also scattered reports of Henoch-Schonlein Purpura (HSP) in association with C2 deficiency (46). The disorder in these situations does not appear to differ from that in C2 replete individuals. Given the extremely common nature of HSP, it is impossible to say whether or not these few reported cases are more than a chance association.

There have been several reports of primary glomerular disease in patients with C2 deficiency who did not have evidence of a systemic process. These would suggest that such deficiency may predispose to immune complex glomerulonephritis through a mechanism other than SLE.

A 1978 study from France (47), for example, reported a family of which several siblings had C2 deficiency associated with a variety of renal disorders. The problem with this report is that the renal lesions were not well characterized (only one underwent kidney biopsy) and appeared to be very different. One, for example, appears to have had a straightforward episode of acute post streptococcal glomerulonephritis, while another seems to have had focal segmental glomerulosclerosis. It is difficult to link these disparate disorders to a single complement component deficiency.

A better-characterized report in 1980 discussed a 13 year old boy in whom membranoproliferative glomerulonephritis was found in the setting of C2 deficiency (48). The boy had no evidence of systemic disease by exam or serology. This child had a particular malignant course of his nephritis, with progressive renal failure requiring transplantation. The disease recurred in his renal allograft, a somewhat unusual event in a patient with membranoproliferative glomerulonephritis.

5.2. C2 polymorphism

At the protein level, isoelectric focusing permits C2 allele typing. As the number of variants identified by this is small, and as the technique is rather cumbersome, there have been few studies examining C2 polymorphism in disease. The MHC extended haplotype associated most often with SLE and MPGN includes the common (C) C2 variant (20).

6. CONCLUSIONS

Deficiencies and polymorphisms of the complement proteins encoded within the class III region of the MHC have a complex association with a variety of glomerular diseases. In some cases, this association represents simply a linked gene within a disease-associated MHC extended haplotype. In others, the component deficiency per se appears to predispose to disease. While individuals with such deficiencies make up a small proportion of the total population of patients with glomerulonephritis, they may have much to teach us about the underlying immunopathology of these diverse conditions.

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