Anti-C1q in Systemic Lupus Erythematosus

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Abstract

C1q is the first component of the classical complement pathway. C1q can bind IgG in immune complexes making it difficult to discern between IgG in immune complexes binding to C1q and anti-C1q auto-antibodies binding to C1q. Both clinically validated in-house ELISA assays as well as commercial ELISA kits are used for detection of anti-C1q antibodies. Anti-C1q autoantibodies can be detected in a wide range of autoimmune diseases and are highly sensitive for hypocomplementemic uticarial vasculitis. In SLE, anti-C1q are strongly associated with proliferative lupus nephritis, and their absence carries a negative predictive value for development of lupus nephritis of close to 100%. Anti-C1q in combination with anti-dsDNA and low complement has the strongest serological association with renal involvement. The anti-C1q titers correlate with global disease activity scores in patients with renal involvement and higher titers seem to precede renal flares. After the successful treatment of a renal flare, anti-C1q has the tendency to decrease or even become undetectable. The main obstacle to the inclusion of anti-C1q in the classification criteria and clinical management of SLE is the lack of standardized laboratory assays.

Keywords

systemic lupus erythematosus; SLE; lupus nephritis; C1q; anti-C1q

Background

The complement system is composed of a large number of distinct plasma proteins that react with one another to opsonize pathogens and induce a series of inflammatory responses that help to fight infection[1]. It plays an important role in both innate and acquired immunity and has a crucial role in providing a first-line defense against microorganisms. The complement system can be activated via the classical pathway initiated by immune complexes, the alternative pathway activated by bacterial surfaces, or via the mannose binding lectin pathway. The common final result of the activation of any of these diverse pathways is the

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formation of the membrane attack complex that induces lysis of the target cells [2,3]. Complement has many other roles, including influencing appropriate immune responses, disposing of waste in the circulation (immune complexes, cellular debris), and contributing to damage of self-tissue through inflammatory pathways [4,5].

The first component of the classical complement pathway is C1q. C1q is composed of 18 polypeptide chains (6A, 6B, 6C) with a molecular weight of 460 KDa [6]. It is a hexamer composed of globular heads attached to collagen-like triple-helix tails [1,7]. Since C1q must bind to at least two heavy chains in order to change its conformation and activate the classical complement pathway, its activation occurs only after binding to immunoglobulins in the form of immune complexes bound to multivalent antigens [7]. The genes encoding for the A, B, and C chains of human C1q are located within the region 1p34.1–1p36.3 on the short arm of chromosome 1 [8]. Mutations leading to C1q deficiency have been found in all three chains and are recessive in nature [6]. Almost all patients with homozygous C1q deficiency develop a lupus-like syndrome. This is one of the strongest disease susceptibility genes for the development of SLE that has been characterized in humans [9,10].

Historical Perspective

In 1971, in a study that used precipitin reactions of C1q in gel diffusion to detect unknown immune complexes containing gamma-globulin in the sera of patients with SLE, some immune complexes were noted to sediment at 7S, the sedimentation constant of monomeric immunoglobulin G, suggesting the presence of autoantibodies [11]. The 7S fractions were eventually identified as monomeric IgG molecules that specifically interacted with the collagen-like tail of the C1q molecule [12–15]. C1q was then found to have a unique ability to bind to the Fc region of IgG and IgM [15,16], preferentially when aggregated in the form of immune complexes [15,17]. Due to the fact that C1q can bind IgG in immune complexes, it is difficult to discern between IgG in immune complexes binding to C1q and anti-C1q auto-antibodies binding to C1q [18].

Detection Methods

In order to inhibit low affinity binding of immune complexes, the first assays developed for the detection of anti-C1q used high ionic strength conditions (0.5–1.0 M NaCl) [18]. The need to use high-ionic strength buffer was obviated by the introduction of solid phase assays that utilized only the C1q collagen-like region [12,19]. An assay for the detection of autoantibodies against the globular domain of human C1q was introduced for the first time in 2007 [20]. Several commercial assays are currently available for the detection of anti-C1q antibodies [15] but none of them have been approved by the Food and Drug Administration due to lack of prospective studies and unknown inter-test variability. Nevertheless, some of the anti-C1q antibody assays have been used in clinical studies [21–27], and a recent study showed good correlation between a commercial kit with a clinically validated in-house ELISA [28]. Unless otherwise specified, most of the studies referred below used commercial ELISA kits for detection of anti-C1q antibodies.

Pathophysiology

The first direct evidence for a pathogenic role of anti-C1q came from an autopsy study of 12 SLE patients, 5 of which had acute proliferative lupus nephritis [29]. Anti-C1q was extracted from 4 out of 5 autopsy kidneys of patients with acute proliferative glomerulonephritis, but not from any of the other specimens. Treatment with DNase unexpectedly released antibodies to Clq which suggested that the immune deposits contained immune complexes composed of DNA and antibodies to DNA, which then bound Clq and, in turn, antibodies to Clq [29]. The anti-C1q/IgG ratio from the glomerular extract was more than 50 times higher than the ratio in serum. In a recent study [30], a subset of anti-DNA antibodies was shown to bind to the globular head of the C1q molecule.

The strongest evidence for a pathogenic role of anti-C1q relates to the experimental studies of Trouw et al. [27,31] who administered anti-C1q monoclonal antibodies to naive mice resulting in glomerular deposition of C1q and anti-C1q autoantibodies but not in overt renal disease. However, administration of anti-C1q autoantibodies to mice pretreated with C1q-fixing anti–glomerular basement membrane (GBM) antibodies, resulted in a strong synergistic enhancement of renal disease. This was not observed when a non–C1q-fixing anti-GBM preparation was used. The authors concluded that anti-C1q autoantibodies deposit in glomeruli together with C1q but induce overt renal disease only in the context of glomerular immune complex disease. This could explain why anti-C1q antibodies are pathogenic in SLE in contrast to hypocomplementemic urticarial vasculitis where immune complex formation is not a major feature of disease.

Clinical Significance

Among 659 randomly selected individuals between 20 to 79 years of age, anti-C1q antibodies were detected in 4% of patients between 40–49 years of age and 18% of the patients older than 70 [32]. Anti-C1q antibodies have been described in many conditions. They are detected in all patients with hypocomplementemic urticarial vasculitis [33,34], although they do not seem to have a pathogenic role in this entity. Other conditions characterized by high anti-C1q antibody prevalence include SLE (28–60%) [21,35–37], scleroderma (26%), rheumatoid arthritis (19%), undifferentiated connective tissue disease (15%), and Sjögren syndrome (14%) [37]. Anti-C1q antibodies are also seen in 26% of hepatitis C patients and correlate with low complement C4 in this population [38].

The first study that showed an association between anti-C1q autoantibodies and lupus nephritis included 35 patients with biopsy-proven diffuse proliferative or membranous lupus nephritis which showed elevations of the C1q solid phase assay for immune complexes in all the patients with diffuse proliferative nephritis and in 71.4% of the patients with membranous nephritis [39].

The first non-renal associations of anti-C1q in SLE patients were shown in a study of 88 SLE patients in whom significant positive correlations were found between anti-C1q titers and the presence of cutaneous lupus, hypocomplementemia, anti-dsDNA, and circulating

immune complexes. A negative correlation was found with neurological disease manifestations [40].

Since these original observations, the association of anti-C1q antibodies with proliferative lupus nephritis, disease activity, and anti-dsDNA antibodies has been consistently reported, in both adult and pediatric SLE patients [41–46].

In a longitudinal study that evaluated the association between relapses and plasma levels of autoantibodies, forty-three patients were selected from a group of 151 SLE patients: the first 17 patients who developed a renal relapse during the study period, the first 16 patients who developed a relapse in organs other than the kidneys, and 10 randomly selected patients without a relapse of SLE. At the time of SLE flare, anti-C1q were detected by an in-house ELISA in 12 of 17 patients with primarily a renal relapse compared with 6 of 16 patients whose flare was non-renal and two of 10 patients who remained clinically inactive (P < 0.005). All 17 patients with a primarily renal relapse were biopsied to determine the cause, and all 14 patients with increased anti-C1q levels had a proliferative glomerular lesion (WHO class III and IV) [47]. Significant increases in anti-C1q levels prior to the relapse occurred in 10 of 14 patients who developed proliferative nephritis but in only three of 16 patients with non-renal relapses. No significant increases in anti-C1q were noted in the patients with inactive disease. The mean time period between the occurrence of a significant increase in anti-C1q level and renal relapse was 2.3 months [47].

In a longitudinal study of 48 patients with biopsy-proven lupus nephritis, serum C3 and C4 levels, as well as anti–double-stranded DNA, anti-endothelial cell, anti-C1q (detected by in-house ELISA), and anti-phospholipid antibody titers were evaluated in patients with quiescent renal disease (38 samples) and those with clinical evidence of renal activity (23 samples)[44]. Only anti-C1q antibody titers correlated with active renal disease in both univariate (P < 0.0001) and multivariate analysis (P < 0.0001), with a sensitivity of 87% and a specificity of 92%. In all patients, the high anti-C1q Ab titers returned to normal values after treatment-induced remission. No other serological parameter was associated with renal disease activity [44].

In a study of 61 SLE patients [36], 40 of whom had biopsy-proven lupus nephritis, anti-C1q antibodies (detected by in-house ELISA) were present in 44% of SLE patients and in 4% of normal blood donors. Anti-C1q antibodies were found in 60% of patients with lupus nephritis compared with only 14% of SLE patients without nephropathy (P < 0.05). High titers of anti-C1q antibodies were detected in 89% of patients with active lupus nephritis compared with 0% of patients with inactive nephritis.

Comparable data were obtained in a prospective multi-center study [21] of 38 patients with lupus nephritis in which 35 out of 36 patients with active proliferative lupus nephritis were positive for anti-C1q (97.2%), in contrast to only 35% of inactive lupus nephritis patients and 25% of active non-renal patients. Anti-C1q markedly decreased during successful treatment (p<0.005) with persistently high anti-C1q titers in only two patients. Interestingly, these were the only two patients in the cohort who did not have a sustained response to

treatment. Authors concluded that a negative test for anti-C1q almost excludes proliferative nephritis in SLE.

In the Hopkins Lupus Cohort [25], stored sera from 49 SLE patients were chosen to include one visit with proteinuria and one or two without, and were then analyzed for anti-C1, anti-chromatin, anti-dsDNA, anti-ribosomal P, monocyte chemotactic protein-1, vascular cell adhesion molecule, intercellular adhesion molecule and complement. Anti-C1q was the only laboratory biomarker associated with both global and renal activity, as well as the only biomarker associated with the SLICC Renal Activity Score. In another study [48], anti-C1q antibodies were found to strongly correlate with parameters of SLE disease activity during follow-up, in particular with regard to renal involvement.

In a study of 151 SLE patients, which included 77 patients with biopsy proven lupus nephritis [43], 74% of patients with active SLE nephritis were positive for anti-C1q compared to 53% with non-active lupus nephritis and 32% with non-renal lupus. Anti-C1q were found in 33 of 83 patients (39%) without history of renal disease. Nine of the 33 patients with anti-C1q developed lupus nephritis during follow up, with a median renal disease-free interval of nine months.

Importantly, in most of the studies, absence of anti-C1q had a high negative predictive value for the development of a severe lupus nephritis, ranging up to 100% [43,45,49] prompting some authors to suggest that 'there is no lupus nephritis without anti-C1q' [49].

However, although most of the clinical studies have shown a high negative predictive value of anti-C1q for the occurrence of proliferative lupus nephritis [5,45], in a study from Sweden only 11 of 18 (61%) patients with proliferative lupus nephritis were anti-C1q-positive [50]. The presence of anti-C1q was, however, predictive of the histopathological outcome.

Increasing titers of anti-C1q seem to precede renal flares by 2–6 months [47,51,52]. On the other hand, anti-C1q titers decreased with treatment in SLE patients with proliferative lupus nephritis, with a more significant decrease noted in treatment responders compared to non-responders, 77% and 38%, respectively [41]. Serial determination of anti-C1q in SLE patients with renal flares might help to identify treatment responders and define patients remaining at risk for renal relapses [5].

The latest data from the SLICC international cohort [37] confirmed the association of anti-C1q with lupus nephritis with a prevalence of 45.5% in patients with SLE with ACR renal involvement. Younger individuals with SLE were more likely to be anti-C1q positive than older individuals. Patients with anti-C1q were three times more likely to have proteinuria and 2.6 times more likely to have urinary red cell casts. No significant associations were seen with arthritis, cutaneous lupus or hematologic manifestations. Anti-C1q prevalence in SLE patients with, versus without, ACR renal disorder (persistent proteinuria > 0.5 g/24h or proteinuria > 3+, or red blood cell casts) was 45.5% compared to 19.3%, respectively. Odds of SLICC renal involvement were independently 2.3 times higher than in the absence of anti-C1q. Odds of SLICC renal involvement were 15 times higher in the presence of simultaneously positive anti-dsDNA, anti-C1q and low complement than in their absence.

The most recent study of anti-C1q included 107 patients with lupus nephritis [53] whose renal histology at the time of diagnosis and 6–12 months after treatment was correlated with serum biomarkers (anti-dsDNA, anti-nucleosome, anti-ribosome P, anti-C1q antibodies, and C3/C4). High titers of anti-C1q antibodies were an independent predictor that discriminated proliferative from non-proliferative lupus nephritis. Only anti-C1q showed a significant correlation with the amount of proteinuria. No biomarker was predictive of remission.

Conclusion

In summary, anti-C1q autoantibodies can be detected in a wide range of autoimmune diseases and are highly sensitive for hypocomplementemic urticarial vasculitis. In SLE, anti-C1q are strongly associated with proliferative lupus nephritis, and their absence carries a negative predictive value for development of lupus nephritis of close to 100%. Anti-C1q in combination with anti-dsDNA and low complement has a strong serological association with renal involvement. The anti-C1q titers correlate with global disease activity scores in patients with renal involvement and higher titers seem to precede renal flares. After the successful treatment of a renal flare, anti-C1q has the tendency to decrease or even become undetectable. The main obstacle to the inclusion of anti-C1q in the classification criteria and clinical management of SLE is the lack of standardized laboratory assays.

Acknowledgments

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