Autoantibodies antiC1q and systemic lupus erythematosus*

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SUMMARY

BACKGROUND AND OBJECTIVES: AntiC1q autoantibody has been associated with kidney involvement in Systemic Lupus Erythematosus (SLE). We aim to review the pathogenic and diagnostic role of antiC1q in lupus nephritis (LN).

CONTENTS: Researchers observed that human antiC1q antibodies, while bound to C1q on the surface of apoptotic cells, did not bind to C1q complexed with either immunoglobulins or immune complexes. This finding implied that the conformational changes to C1q that reveal the antiC1q-antibody-binding sites depend on the nature of the surface ligand to which the C1q is bound. It could be therefore hypothesized that is binding to C1q complexed with apoptotic cells within the kidney that provides the substrate for antiC1q antibodies to amplify complement-mediated renal injury and the strong renal tropism of antiC1q-antibody-mediated tissue injury. Prospective studies were able to demonstrate that the occurrence of LN was associated with high levels of antibodies antiC1q which fell significantly after immunosuppressive therapy and no occurrence of LN in those patients with SLE antiC1q negative, Negative Predictive Value as high as 100% for the test in question also were shown. When AntiC1q; dsDNA, C3 and C4 were compared for the prediction of proliferative forms of LN, antiC1q showed better sensitivity and specificity among all tested.

CONCLUSION: Enough evidence exists that the dosage of AntiC1q is recognized as an important tool, noninvasive and should be used in a regular way to assess the diagnosis of LN.

Keywords: AntiC1q autoantibodies, Lupus nephritis, Systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease, presenting heterogeneous clinical manifestations that can range from skin rashes, arthralgia, serositis, nephritis, central nervous system involvement, with varying degrees of severity.

The most likely source of autoantibodies in lupus is cellular debris resulting from apoptosis. The vesicles exhibit apoptotic intracellular molecules on their surface that normally are not presented to the immune system, such as nucleosomes, SSA, SSB, among others. Antibodies against these substances are common in patients with SLE, and have been associated with the develop-
ment of skin lesions and extracutaneous manifestation. The C1q is the first component of the classical pathway of complement activation and its main function is to remove tissue and immune “self” antigens generated during apoptosis. Homozygous deficiency of C1q can almost be considered a monogenic form of SLE, since 93% of these patients have manifestations of SLE or “lupus-like”. The lupus nephritis (NL) is one of the most feared clinical manifestations due to its poor prognosis. About 15% to 20% of cases progress to the End Stage Renal Disease (ESRD) in a period of 10 years, 50% to 60% go into remission in five years and 15% of these patients die within 5 years. The rates of ESRD secondary to NL increased from 1.16 to 3.8 cases pmp from 1982 to 1995.

Anti-C1q antibodies were first recognized in 1971. They were identified more frequently in patients with SLE, but the highest titers were found in patients with hypocomplementemic urticarial vasculitis syndrome (HUVS), which is closely related to SLE. C1q antibodies have been strongly associated with kidney involvement in SLE. The main hypothesis to explain the pathogenesis of Anti C1q antibodies in SLE is that the disease is exacerbated by a decrease in the clearance of apoptotic cells. In this scenario it is plausible that the C1q binding to the surface of the body became an apoptotic antigen itself, similar to nuclear components that are not normally exposed to the system immune. Anti-C1q antibody fragments were isolated from glomerular basement membrane in patients with proliferative lupus nephritis and deposition seemed to occur via binding to C1q. In a recent study in mice it has been shown that injecting anti-C1q alone resulted in glomerular deposition of antibody and C1q, as well as mild influx of neutrophils, but did not cause severe kidney damage. However, when immune complexes were induced by a pre-injection of nephritogenics doses of anti-glomerular basement membrane (anti-GBM), there was exacerbation of subclinical renal disease after injection of anti-C1q. Siegert et al. in a prospective study demonstrated a temporal association between elevated titers of IgG AntiC1q and development of proliferative glomerulonephritis in SLE, suggesting that serial measurements of these antibodies are a valuable tool in managing these patients.

Renal biopsy is the gold standard for diagnosis of NL, but because of its possible complications, this invasive procedure can not be repeated so often. In this context, monitoring of anti-C1q antibodies may represent a noninvasive biomarker useful in monitoring patients with SLE.

THE C1q COMPLEX AND COMPLEMENT SYSTEM

The complement system is a central component of the innate immunity and one of the major effectors mechanisms of antiboody-mediated immunity. It has three main physiologic activities: defending against infections, bridging innate and adaptive immunity, and clearing immune complexes and apoptotic cells. Complement proteins are plasma and cell surface proteins that are normally inactive and become activated after they are attached to microbes or antibodies. The complement system exhibits three pathways of activation: (1) the classical pathway; (2) the alternative pathway and (3) the lectin-mediated.

C1q, a key component of classical pathway, is actually a complex of three proteins: C1q, C1r, and C1s. C1q is a collagen-like component that is able to bind antibodies but only after the antibody has been bound to a foreign or self antigen. Once C1q is bound to the Fc antibody, C1r and C1s are sequentially cleaved and released, after which the rest of the classical pathway is activated.

Deficiencies in classical pathway components are associated with bacterial infections, but also with the occurrence of systemic lupus erythematosus (SLE), the prototype of a systemic autoimmune disease. Homozygous deficiency of C1q, C1r and C1s, and C4 are strongly associated with susceptibility to SLE. C1q deficiency is the strongest disease susceptibility gene for the development of human SLE.

C1q contains six distinct globular heads and a unique collagen-like region. Auto antibodies to C1q were first identified in the serum of patients with Systemic Lupus Erythematosus as C1q precipitins. It is now well-established that anti-C1q antibodies are mostly IgG isotype, and the epitopes recognized are on the collagen-like region (CLR) of C1q.

WASTE DISPOSAL HYPOTHESIS FOR SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic Lupus Erythemathosus is characterized by the occurrence of a variety of autoantibodies, B-cell hyperactivity and immune complex formation. A more recent theory on the pathogenesis of SLE is the so called waste disposal hypothesis. This hypothesis assumes that SLE is driven by a defective clearance of dead and dying cells that could become antigenic and provoke an autoimmune response. Several studies provide support for this hypothesis: mice with a defect in the clearance of apoptotic cells were shown to develop severe autoimmunity with the occurrence of autoantibodies directed against nuclear components, as seen in SLE patients. Lupus-prone mice were shown to have an impairment of apoptotic cell uptake and macrophages derived from SLE patients were also shown to have a defective uptake of apoptotic cells. A number of lupus antigens could be located on the surface of apoptotic bodies and apoptotic blebs and it was demonstrated that injection of an excess of apoptotic cells into healthy mice led to the production of autoantibodies and it was demonstrated that injection of an excess of apoptotic cells into healthy mice led to the production of autoantibodies. Therefore, it seems that apoptotic cells are the source of autoantigens that drive the autoimmune response in SLE.

C1q has been described to bind to apoptotic cells and to promote their clearance either directly or by complement activation. These reports were supported by the finding that C1q deficient mice have a delayed clearance of apoptotic cells and an accumulation of apoptotic bodies in the glomeruli. Homozygous C1q deficiency is the strongest disease susceptibility gene in human SLE, suggesting that complement, and especially C1q, is involved in the prevention of autoimmunity through its role in the clearance of dead and dying cells. However, although hypocomplementemia is frequently found, most SLE patients do not have primary C1q deficiency but other links between C1q and SLE exist. Hypocomplementemia in SLE patients usually is due to consumption of C1q and other components of the classical pathway of complement, in particular during flares. In addi-
tion, C1q is deposited in affected tissues, such as the skin or the kidney. Auto antibodies against C1q (anti-C1q) develop in about one third of SLE patients and they are associated with complement consumption. Anti-C1q were shown to strongly correlate with the occurrence of biopsy-proven active lupus nephritis and severe forms of lupus nephritis are rare in the absence of anti-C1q. Therefore anti-C1q is believed to have a pathogenic role in SLE.

Anti-C1q cannot be depleted by fluid phase C1q, suggesting that they bind to a neoeptope that is only expressed upon conformational changes that occur when C1q binds to a target structure. Trendelenburg et al. observed that human antiC1q antibodies, while bound to C1q on the surface of apoptotic cells, did not bind to C1q complexed with either immunoglobulins or immune complexes. This finding implied that the conformational changes to C1q that reveal the antiC1q antibody-binding sites depend on the nature of the surface ligand to which the C1q is bound. This novel concept suggests that modifications of C1q bound to apoptotic cells generate the antiC1q antibody binding sites. It could therefore be hypothesized that is binding to C1q complexed with apoptotic cells within the kidney that provides the substrate for antiC1q antibodies to amplify complement-mediated renal injury and the strong renal tropism of antiC1q-antibody-mediated tissue injury.

ASSOCIATION BETWEEN AUTOANTIBODIES ANTI-C1q AND SYSTEMIC LUPUS ERYTHEMATOSUS

Anti-C1q autoantibodies were first recognized in 1971. They were mostly found in patients with SLE but the highest titers were observed in patients with the Hypocomplementemic Urteric Vasculitis Syndrome (HUVS), which is closely related to human SLE. Anti-C1q autoantibodies have been reported to bind with high affinity and via the F(ab) fragments to the collagen region of the C1q molecule.

Although antiC1q are associated with lupus nephritis and more preferably located in the glomeruli of SLE patients, their pathophysiological significance has remained unclear. It also remains the question of this class of autoantibodies just be an epiphenomenon or actually be pathogenic, and being, how and in what clinical circumstances it would. Regarding this issue, Trow et al developed an experimental murine mAb JL-1, which was identified by ELISA based on their ability to recognize the domain of the tail of C1q. When AntiC1q JL-1 was administered alone, this was linked to the C1q in the glomeruli, which normally present at low levels. This interaction was insufficient to induce significant glomerular damage. However, when JL-1 was administered to mice in which the levels of C1q in the glomerulus were sufficiently high as a result of its interaction with other antibodies with specificity for glomerular antigens, then the mice showed significant glomerular damage shown by a reduction in their renal function and high leakage of urine protein. In this context, anti-C1q antibodies could interfere with the ability of C1q to recognize apoptotic fragments containing DNA and other nuclear autoantigenes, so the mice became prone to develop SLE, similar to what occurs when there is lack of genetic C1q.

Some recent studies such as the Siegert et al. and Moura et al. have documented evidence of significantly higher titers of anti-C1q in SLE patients with renal dysfunction compared with patients with involvement of other organs as summarized in the table below (Table 1).

<table>
<thead>
<tr>
<th>References</th>
<th>Anti-C1q positive with LN</th>
<th>Anti-C1q positive without LN</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Siegert et al.</td>
<td>15/21 (71%)</td>
<td>14/47 (30%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Moura et al.</td>
<td>13/32 (40.6)</td>
<td>9/49 (18.4%)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Marto et al. showed in a representative sample of patients with lupus that antiC1q is useful to identify a subgroup of patients at risk of developing lupus nephritis and that monitoring of such antibodies is potentially more important in the prediction of renal flares than the activity disease indices currently employed. Gunnarsson et al. and Fremeaux-Bacchi et al. found that Anti-C1q had a significant inverse correlation with levels of C1q, C3 and C4, and decreases in these components of the classical pathway are associated with active renal disease.

Trendelenburg et al. in a prospective, multicenter trial investigated 38 adult patients with SLE who underwent renal biopsy for suspected active lupus nephritis. Serum samples were taken at the time of biopsy and analyzed for the presence of anti-C1q. 36 patients had proliferative forms (Class II, III or IV) and two had class V lupus nephritis. All except one patient with proliferative lupus nephritis were positive for anti-C1q (97.2%) compared with 35% of SLE patients without renal manifestations. The evidence of anti-C1q decreased markedly after immunosuppressive treatment. They conclude that the antibodies Anti-C1q have a very high prevalence in active lupus nephritis proven by biopsy, so a negative result virtually excludes active nephritis (Table 2).

The data support the hypothesis of a pathogenic role of anti-C1q in lupus nephritis.

Moura et al. found in a cross-sectional study that high levels of antiC1q were strongly associated with biopsy-proven lupus active nephritis and decreased markedly after one month of aggressive immunosuppressive treatment. All 15 cases of lupus nephritis patients had proliferative forms (Class III or IV) and important clinical findings (Table 3). The authors concluded that Negative Predictive Value (NPV) of such a test for this clinical condition is very high (Table 2) and may have an influence on treatment decisions, including being able to reduce the number of indications of renal biopsies.

Moroni et al. in a prospective study involving 228 patients with lupus nephritis dosed antiC1q: dsDNA, C3 and C4 for six years and correlated with development of active lupus nephritis. In proliferative forms of LN in the absence of antiphospholipid antibodies, antibodies antiC1q showed better sensitivity and specificity among all tested (80.5 and 71% respectively). In univariate analysis, antiC1q was the best predictor of LN activity (p < 0.005). In multivariate analysis, the association of antiC1q, C3 and C4 were the best predictors of activity of LN (p < 0.0005, p < 0.005 and p < 0.005 respectively) (Table 2).
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Table 2 – Sensitivity, positive-predictive value (PPV) and negative predictive value (NPV) of antiC1q antibodies for renal flares in different studies

<table>
<thead>
<tr>
<th>References</th>
<th>LN patients number</th>
<th>Sensitivity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marto et al.1</td>
<td>77</td>
<td>ND</td>
<td>27%</td>
<td>100%</td>
</tr>
<tr>
<td>Trendelenburg et al.10</td>
<td>38</td>
<td>97%</td>
<td>.68%</td>
<td>98%</td>
</tr>
<tr>
<td>Moura et al.11</td>
<td>15</td>
<td>86.7%</td>
<td>56%</td>
<td>94.6</td>
</tr>
<tr>
<td>Moroni et al.12</td>
<td>228</td>
<td>81%</td>
<td>38%</td>
<td>94%</td>
</tr>
</tbody>
</table>

LN = lupus nephritis; PPV = positive-predictive value; NPV = negative predictive value.

Meyer et al.13 found that antiC1q negative patients were in very low risk of developing lupus nephritis (100% Negative Predictive Value) and those with positive antiC1q had a risk of about 50% of developing lupus nephritis in the next decade and therefore needed constant monitoring.

CONCLUSION

Although the exact role of autoantibodies antiC1q in the pathogenesis of SLE is still unknown, a growing number of scientific evidence has demonstrated its association with active lupus nephritis in both experimental studies in mice, as well as in observational studies in humans confirmed by renal biopsy. Prospective studies were able to demonstrate that the occurrence of severe forms of lupus nephritis was associated with very high levels of antibodies antiC1q which fell significantly after immunosuppressive therapy and no occurrence of LN in those patients with SLE antiC1q negative, Negative Predictive Value (NPV) as high as 100% for the test in question also were shown. When AntiC1q; dsDNA, C3 and C4 were compared for the prediction of proliferative forms of LN in a prospective way, the antibodies antiC1q showed better sensitivity and specificity among all tested (80.5 and 71% respectively). In univariate analysis, antiC1q was the best predictor of activity in the LN and in multivariate analysis, the association with antiC1q, C3 and C4 were the best predictors of activity of LN. Enough evidence therefore exists that the dosage of AntiC1q is recognized as an important tool, noninvasive and in conjunction with clinical examination findings and other laboratory tests, should be used in a regular way to assess the diagnosis and prognosis of patients with SLE.

REFERENCES

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