

ETIOPATHOGENESIS OF VIRUS RELATED GLOMERULOPATHIES

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SUMMARY : *Immune mechanisms, especially immune complex deposition within glomeruli, have an important role in the pathogenesis of most cases of glomerulopathies. One of the most common triggering factors of immune reactions in the host is viruses. Since viral infections are associated with some degree of immune complex formation, they have been implicated in the pathogenesis of glomerular injuries. It has been shown that a virus can induce both specific antibody formation against the components of virus itself, as in the case of hepatitis B virus, and autoantibody to the host components due to molecular mimicry with viral antigens or structural alterations induced by virus, which is the case in Epstein Barr virus infections. Apart from immune complex formation, viruses can also lead to glomerular disease either by stimulating other immunologic reactions (such as activation of cytokines or cell adhesion molecules) or by direct cytopathic effect on the host cells which explains, at least partially, glomerular lesions associated with human immunodeficiency virus infection. It appears that histopathological renal involvement is fairly common during the course of viral infections, although clinically apparent renal disease is rare.*

Key Words : *Virus, Glomerulopathy.*

INTRODUCTION

After Combes and associates demonstrated the deposition of hepatitis B surface antigen (HBsAg) and anti HBs along the glomerular capillary basement membrane in a patient with acute hepatitis B virus (HBV) infection and membranous nephropathy in 1971 (1, 2), and thus recognized the pathogenetic association between HBV infection and glomerulonephritis, there have been increasing interest on the etiologic and pathogenetic roles of viruses in glomerular diseases.

It is known that immune mechanisms play roles in the pathogenesis of most cases of the glomerulopathies. Although other immune mechanisms may

be involved in these pathologies, antibody-mediated glomerular injury is the most important mechanism. There are two forms of antibody-mediated glomerular injury : In situ immune complex (IC) formation and deposition of the circulating immune complexes within the glomeruli. In the former, antibodies directly react with the host antigens (e.g., antigens localized within the glomerular basement membrane) or the exogenous antigens bound to glomerular structures (e.g., virus-specific antigens). But these type of reactions are responsible for a very small part of glomerulopathies in humans. Glomerulopathies related to circulating ICs are due to the trapping of ICs within the glomeruli and activation of the complement system. These

ICs may contain such antigens as bacterial products, virus specific antigens, tumor associated antigens etc. (3).

Circulating ICs are formed to some extent during almost all acute and chronic viral infections (4). Although viral infections are so common in humans, overt glomerular injury in association with these infections are seen rarely. This discordance may be explained as follows : a) Genetic structure of the host (especially major histocompatibility antigens are important: for example HBV infection tends to follow a chronic course in individuals carrying HLA-DR3 antigen and unresponsiveness to HBV vaccine is more common in these cases (5)) and associated events (complement activation, cytokine production etc.) play roles in the development of glomerular injury. b) Overt glomerular disease develops in only a fraction of the patients with morphologic glomerular injury. c) IC formation and renal disease development is facilitated by persistence of the viral infection (ICs deposited in kidney are cleared by monocytes and mesangial cells and thus inflammatory changes subside, such as seen in poststreptococcal glomerulonephritis cases. However, if a continuous antigen supply is provided, then continuous IC formation, deposition and progressive glomerular injury may develop (3)).

Glomerular injury mechanisms seen during the course of viral infections are summarized in Fig 1.

The following criteria must be fulfilled to prove that a particular glomerulopathy is caused by chronic viral infection (1) : 1) The same pathology can

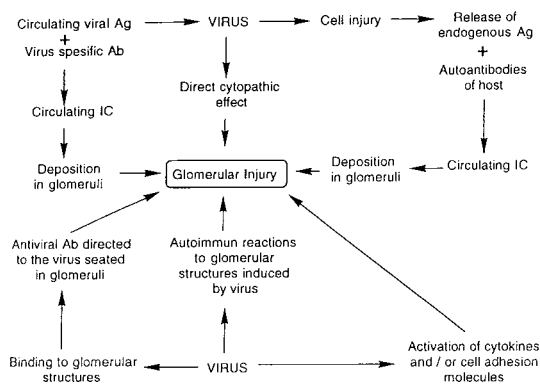


Fig - 1 : Glomerular injury mechanisms in viral diseases.

be produced in experimental animals infected with that virus. 2) Virus specific antigen (s) should be demonstrated in the glomerulus. 3) The pathology should disappear with eradication of the virus. Unfortunately, there is not yet a satisfactory research report of glomerulonephritis produced in experimental animals. Furthermore, since renal biopsy can not be performed in patients with clinical remission because of ethical rules, complete disappearance of the pathology with viral eradication is not easily demonstrated. So, at present, diagnosis of virus related glomerulonephritis depends on the demonstration of virus specific antigen (s) in the glomeruli.

For a virus to be implicated as the cause of glomerular injury due to circulating ICs, the following criterias should be included (4) : 1) Demonstration of immunoglobulin deposits in glomeruli by immunofluorescence microscopy and electron dense deposits in the glomerular capillaries or mesangium by electron microscopy. 2) Demonstration of viral antigens in the same distribution as the immunoglobulin deposits by immunofluorescence or immunoperoxidase. 3) Detection of ICs containing viral antigen and its specific antibody (preferably of the same type as the deposited immunoglobulin).

Table 1 summarizes some of the viruses implicated in the pathogenesis of glomerular lesions associated with these viruses.

In chronic HBV infection ICs containing viral antigens are formed in the circulation, deposit in glomeruli and provoke glomerulonephritis. Thus, it is a prototypic example of viral induced immune complex disease (4). Researches up to date showed that during the course of chronic HBV infection several distinct glomerular pathology types may be seen and in a particular pathology there is deposition of a particular HBV antigen within glomeruli. This is because of the different molecular weights of the different HBV antigens. Whereas HBs Ag and HBeAg have a molecular weight of over 2 billions. HBeAg has two forms with molecular weights of 19,000 and 300,000. It was shown experimentally by immunization of rabbits with bovine serum albumin that small ICs were deposited on the epithelial side of the glomerular basement membrane, whereas the larger ICs were deposited mainly in the mesangium. Thus, this can explain why we see HBeAg in membranous nephropathy and HBsAg in proliferative or mesangiocapillary glomerulonephritis.

Virus	Associated renal pathology	Clinical features
HBV	Membranous nephropathy Membranoproliferative GN IgA nephropathy Mesangioproliferative GN Focal GS Polyarteritis nodosa Minimal change disease	Clinical hepatic disease may not be obvious Usually improves with seroconversion to anti-HBe
HCV	Membranoproliferative GN	Always accompanied with advanced liver disease
HIV	Focal GS Interstitial nephritis Mesangial hyperplasia Minimal change disease	Usually late findings of the disease Nephropathy incidence is 7.7 % Abnormal urinalysis (most commonly proteinuria) is found in 40-60 %
EBV HSV CMV	IgA nephropathy	Autoantibody induction due to molecular mimicry
Hantavirus	Hemorrhagic fever with renal syndrome	Acute viral infection Predominant tubular pathology Glomerular injury is rare

Table 1 : Some of the viruses mentioned in the text and associated renal lesions (HBV : Hepatitis B virus, HCV : Hepatitis C virus, HIV : Human immunodeficiency virus, EBV : Epstein Barr virus, CMV : Cytomegalovirus, HSV : Herpes simplex virus, GN : Glomerulonephritis, GS : Glomerulosclerosis).

The best recognized glomerulopathy associated with chronic HBV infection is membranous nephropathy (HBV-MN) (1). HBeAg is the most important antigen which plays role in the development of HBV-MN (6). In children, HBV related glomerulopathy is almost always this type. Other HBV related glomerulopathies are rare in children (1). In pediatric population HBV-MN is usually suspected by routine urine and serologic screening, since they are generally asymptomatic. But HBV-MN may present as a nephrotic syndrome mimicking minimal change disease with a relapsing course. In this clinical form, while there is a 30 to 60 % spontaneous regression rate within one year, proteinuria persists in the rest. Remission of proteinuria is generally associated with seroconversion to anti-HBe. Close correlation between the decrement in serum HBeAg level and improvement of proteinuria suggests that HBV glomerulonephritis is the result of persistent antigen supply originating from active viral

replication in the liver (6). But, in one report, it is stated that only serum HBeAg status in persistent HBsAg carriers is not correlated with the remission rate and the remission is seen usually before HBeAg-antiHBe seroconversion develops (7). These results imply that there may be some factors, other than HBeAg, playing roles in the pathogenesis of HBV membranous nephropathy. We have also experience concerning an eight year old boy with anti-HBe antibody who had histopathologically proven HBV related membranous nephropathy (8).

Other forms of glomerulopathies that may be seen in chronic HBV infection are mesangiocapillary glomerulonephritis, mesangioproliferative glomerulonephritis with predominant mesangial IgA deposits, focal glomerulosclerosis, and polyarteritis nodosa (PAN). All these pathologies are more common in adults (1).

Chronic HCV infection has also found to be re-

lated to cryoglobulinemia and MPGN (9, 10). Immune complex nephritis seen in these patients may be related to the formation and deposition of immune complexes containing HCV, anti-HCV IgG and IgM rheumatoid factors. Advanced liver disease has been reported in all the patients with HCV-MPGN.

In some viral infections, since viral antigens may share amino acid sequences with host tissue antigens, autoantibodies may be stimulated by molecular mimicry as in the case of Epstein Barr virus (EBV), HBV and polio virus infections. Apart from EBV, other herpes group of viruses, namely cytomegalovirus and herpes simplex virus, have also been implicated in the pathogenesis of glomerular lesions of IgA nephropathy (11). Another clinical example of this mechanism is Kawasaki disease. This possibly viral disease has been found to be associated with auto endothelial antibody and auto antineutrophil cytoplasmic antibody and both of these antibodies have been implicated in the pathogenesis of vasculitis and renal disease (4). Hantavirus, etiologic agent of hemorrhagic fever with renal syndrome, has been suggested to cause renal disease due predominantly to the tubular dilatation and interstitial edema and rarely to the glomerular injury (12).

Renal pathology in Human immunodeficiency virus (HIV) infection is due to the direct viral invasion of and cytopathic effect on the glomerular and tubular cells (4). Although the incidence of nephropathy is 7.7% in patients with acquired immunodeficiency syndrome (AIDS), 40-60 % of patients have abnormal urinalysis, mostly persistent proteinuria. Focal glomerulosclerosis and tubular interstitial nephritis are seen pathologically. Mesangial hyperplasia, focal necrotizing glomerulonephritis and minimal change disease have also been reported. Although direct tubular invasion has been implicated as the pathogenetic mechanism due to the finding of HIV nucleic acid in tubular cells on biopsy specimens, some authors suggest that circulating immune complexes are responsible for this pathology. During the course of HIV infection, patients may also have proximal and/or distal renal tubular acidosis (13).

In summary, it is considered that during the course of many acute and chronic viral infections there seems to be much more common subclinical glomerular and/or tubular injury than the clinically apparent cases and this injury is related primarily to

the various immunologic injury mechanisms initiated by the virus itself. But, genetic structure of the host and the immune system based on this structure are also important in the development of clinically apparent renal disease.

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