

The Nephritis Associated with Viral Infections

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Abstract

Renal involvement associated with various viruses has been identified, with each associated with a different disease type. Accumulated studies have revealed the pathogenesis and optimal therapies of nephritis associated with viral infections. This review focuses on the nephritis associated with viral infections.

Introduction

Renal involvement associated with several viruses has been identified, with each associated with a different disease type. The pathogenesis and optimal therapies of renal involvement associated with virus infections have been increasingly understood through previous studies.

The mechanism of renal involvement by virus infections

The mechanism of development of renal involvement associated with viral infections can be categorized into those by direct effects of renal parenchymal infection and those by immune response to extra renal infection [1]. In the former type, renal injury is caused by cytomegalovirus, herpes simplex virus, adenovirus, hantavirus, BK virus and a part of human immunodeficiency virus (HIV). In this type, direct toxicity of viruses and/or antibody (Ab) reactions against antigens (Ag) of viruses that infect the kidney causes renal injury [2,3]. The latter type of renal injury is caused by hepatitis B virus (HBV), hepatitis C virus (HCV), a part of HIV and parvovirus B19. In this type, the depositions of Ag-Ab complexes called immune complexes, which are produced in the extra renal space by Ab reactions against Ag of the virus, cause renal injury [2,3].

HBV-associated nephritis

HBV is transmitted through human blood and body fluids. HBV infection may cause not only hepatitis, but also a variety of renal diseases, including membranous glomerulonephritis (MN), membranoproliferative glomerulonephritis (MPGN) and polyarteritis nodosa [4,5]. MN associated with HBV infection, which often causes nephritic syndrome, has been reported most frequently. It has been proposed that the deposition of HBe Ag and anti-HBe Ab complex is responsible for the formation of pathogenic subepithelial immune deposits [6]. Through the seroconversion from HBe Ag to anti-HBe Ab, spontaneous resolution of nephritis is most common in infantile cases; however, it is relatively uncommon in adults [5,7,8]. MPGN associated with HBV infection has also been reported. The deposition of circulating HBe Ag or HBs Ag-anti HBs Ab complexes in the mesangial area and subendothelial space characterizes the MPGN associated with HBV infection [6]. Corticosteroids and other immunosuppressants have been used as the basic treatment for HBV-associated nephritis [9]; however, there is little consensus about the optimal choice of such agents for the treatment of HBV-associated nephritis among HBsAg carriers, since the treatment might enhance viral replication and precipitate hepatic flares due to reactivation of hepatitis [10-13]. The use of antiviral drugs and interferon has also been reported for the treatment of HBV-associated nephritis; however, there are limited data on this. Interferon therapies have less resistance, but may be indicated in younger patients with normal renal function because of side effects such as fever, listlessness, myalgia and depression. Conjeevaram et al. [14] reported that 15 HBV-associated nephritis patients were treated

by interferon- α therapy and 8 patients had a long-term serological response with sustained loss of serum HBe Ag and HBV DNA, and 7 of 8 of those patients also showed marked improvement in proteinuria [14]. Tang et al. reported that lamivudine treatment improves renal outcome in HBV carriers with MN [15].

HCV-associated nephritis

Various types of glomerular nephritis such as MN, Focal Segmental Glomerulosclerosis (FSGS), proliferative glomerulonephritis and fibrillary and immunotactoid glomerulopathies have been recognized as being associated with HCV infection [16-19]. The deposition of HCV Ag - anti-HCV Ab complexes in the glomerulus is thought to be responsible for HCV-associated nephritis [20]. In addition, the deposition of mixed cryoglobulin, which is characterized by monoclonal immunoglobulin (IgM κ) and polyclonal immunoglobulin (IgG), produced in association with HCV infection in the glomerulus occasionally causes nephritis. MPGN is most frequently observed by the deposition of mixed cryoglobulin.

Antiviral therapy with interferon alpha or pegylated interferon has been reported to be effective for HCV-associated nephritis [19]. Johnson et al. [19] reported that 6 to 12 months of interferon alpha treatment was effective for HCV-associated MPGN with or without cryoglobulinemia in 14 patients. In this study, proteinuria was decreased in association with the disappearance of HCV RNA from the plasma [19]. In addition, an anti-viral drug, rivabirin, improves the sustained virologic clearance when given in combination with interferon. Alric et al. [21] reported that 12 of 18 patients showed improved HCV-associated glomerulonephritis associated with HCV RNA clearance (sustained virological response) by the combination therapy of regular or pegylated interferon alpha and ribavirin. Recently, the effectiveness of therapy with rituximab, which is a chimeric monoclonal Ab against the protein CD20, for HCV-associated mixed cryoglobulinemia has been reported [22].

HIV-associated nephritis

FSGS is a relatively common complication in patients infected with HIV; however, an increasing number of different forms of renal disease

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Received December 05, 2011; Accepted December 11, 2011; Published December 13, 2011

Citation: Numata A, Morishita Y, Kusano E (2011) The Nephritis Associated with Viral Infections. J Nephrol Therapeutic S3:003. doi:10.4172/2161-0959.S3-003

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such as MN, MPGN, amyloidosis, interstitial nephritis and thrombotic thrombocytopenic purpura have been observed [23-25]. The severity of nephritis is a critical factor for mortality and worse outcome in HIV-infected patients [26,27]. The mechanism of HIV-associated nephritis has not been fully revealed. The deposition of HIV Ag – anti-HIV Ab complexes in the glomerulus is thought to contribute to the development of HIV-associated nephritis. Although HIV is considered to be able to infect glomerular endothelial cells, mesangial cells or tubular cells, it has not been well determined whether HIV itself plays a direct role in the development of renal injury [28-30]. Studies on animal models suggested that cytokines such as fibroblast growth factor and transforming growth factor-beta may play a role in the matrix accumulation, fibrosis and tubular injury associated with HIV-associated nephritis [31,32]. Therapy with a combination of antiretroviral drugs, typically three or four, known as highly active anti-retroviral therapy (HAART), has been thought to be effective for HIV-associated nephritis. Schwartz et al. [33] reported that HAART reduced the rate of progression from HIV-associated nephritis to end-stage renal disease. Lucas et al. [34] reported that HAART may prevent the development of HIV nephritis. ACE inhibitors may also have beneficial effects for HIV-associated nephritis in terms of proteinuria and long-term renal survival [35,36]. Corticosteroids or other immunosuppressants have been considered for treatment of HIV-associated nephritis [37,38].

Human parvovirus B19-associated nephritis

Glomerulonephritis associated with parvovirus B19 infection has been reported, and most of these cases are in females. The deposition of human parvovirus B19 Ag – anti-human parvovirus B19 Ab complexes in the glomerulus is thought to be responsible for human parvovirus B19-associated nephritis. Histological examinations of the kidney demonstrated endocapillary proliferative glomerulonephritis in most cases and spontaneous resolution is commonly observed. In several cases, the involvement of parvovirus B19 has been proven by immunohistochemistry or by detecting parvovirus B19 DNA from renal biopsy specimens [39,40].

Hantavirus-associated nephritis

Hantavirus-associated nephritis showed proteinuria, hematuria and reduced renal function. The most prominent renal histopathologic change is acute tubulointerstitial nephritis [41]. The mechanism of the renal involvement is considered to be not only damage to endothelium by the virus, but also damage to tubulointerstitium by cytokines [42,43]. However, the clinical course can be extremely variable and some infected patients are asymptomatic, while some patients with severe cases progress to shock and oliguric acute renal failure sequentially from fever with hemorrhage [44]. Although some patients may have persistent proteinuria or hypertension, most recover kidney function without any specific drug [44].

BK virus-associated nephritis

BK virus infection causes tubulointerstitial nephritis and ureteral stenosis in renal transplant recipients [45]. The mechanism of renal involvement by BK virus is considered to involve direct damage to infected urothelium of BK virus [45]. An increased incidence of BK virus infections in renal transplant recipients is associated with an increased degree of immunosuppression [45]. The clinical features of BK-associated nephritis most closely resemble those of acute rejection, which may be accompanied by fever [46-49] (Table 1).

Other virus-associated nephritis

Many other viruses such as cytomegalovirus, herpes simplex virus

Virus	Disease type
HBV	MN
	MPGN
HCV	MN
	MPGN (mixed cryoglobulin)
HIV	FSGS
	MN
	MPGN
	tubulointerstitial nephropathy
	amyloidosis
Human parvovirus B19	endocapillary proliferative glomerulonephritis
Hantavirus	tubulointerstitial nephritis
BK virus	tubulointerstitial nephritis

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MN, membranous glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; TTP, thrombotic thrombocytopenic purpura

Table 1: The nephritis with viral infections.

and adenovirus may also cause renal involvement by a direct or indirect mechanism.

Conclusion

Various virus infections cause several types of nephritis. Several drugs have been reported to be effective for treatment of virus infection-associated nephritis. However, the choice of drugs as well as their use in the treatment of virus infection-associated nephritis has to be carefully determined considering the possibility that those drugs may exacerbate renal damage. Further studies are still needed to confirm the mechanism and treatment of virus infection-associated nephritis.

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This article was originally published in a special issue, [Clinical Nephrology](#) handled by Editor(s), Dr. Samy L Habib, The University of Texas Health Science Center, USA