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Features of the Clinical Course of Virus-Associated Glomerulonephritis in Children and Adolescents

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Annotation: This article provides a review of the literature on the results of studies to identify etiopathogenetic factors, clinical course, features of diagnosis and treatment of glomerulonephritis in children. According to extensive literature, viral infections are temporarily associated with the onset of many glomerular diseases, especially in children. In other cases of glomerulonephritis, where the infection is clinically asymptomatic, viral syndromes may still be implicated as a trigger. However, convincing evidence for the viral etiology of most glomerular diseases is still lacking.

Key words: virus, glomerulonephritis, nephropathy, pediatrics, pathology, glomerular diseases, children, bacteria, nephrotic syndrome, urine test.

Relevance

Viral syndromes are often considered likely triggers of autoimmune diseases. Studies in pediatric cohorts also support this association in acute glomerulopathies. A prospective Canadian study linked 71% of nephrotic syndrome (NS) exacerbations to a specific viral respiratory infection [1]. In this study, 32 children with UA were followed for two years with repeat cultures and daily urine tests. Within 10 days of many relapses, infections with respiratory syncytial virus (RSV), influenza, parainfluenza, varicella, or adenovirus were identified. Similarly, in a prospective cohort of ten children with hemolytic uremic syndrome (HUS), eight had evidence of adenovirus or enterovirus infection, and the other two had culture-positive family contacts [2]. Although no strain of the virus causes any specific renal pathology, some glomerular diseases are associated with infection or antiviral responses of the host. [3]. Most of these association studies are dated and include small numbers of patients. Now that new molecular diagnostic techniques are available, many classifications of glomerular diseases have been revised, and vaccines have changed the nature of viral infection, reexamination of these associations is warranted. Ultimately, pediatric nephrologists may find that the outcomes of virus-associated glomerulopathies differ significantly from those of truly idiopathic forms [4]. According to the International Committee on Taxonomy of Viruses, there are seven orders, 103 families, 455 genera, and more than 2,800 species of viruses. Although only a subset of these species are known to infect humans, the number of human viral pathogens continues to increase. Viruses are generally polytropic, affecting multiple tissues or organ systems. Kidney cells are often infected during viral illnesses, but appear to be unusually resistant to damage compared to other organs and tissues. Both viruria and viremia are often measurable in viral syndromes. Human kidney cells are commonly used to culture several viruses in the laboratory, including adenovirus, cytomegalovirus (CMV), coxsackievirus, measles and varicella viruses [3]. The kidneys rarely bear the brunt of infection, either due to cytotoxic effects or host antiviral responses, unlike viral arthritis, hepatitis, meningitis, otitis media, pharyngitis, pericarditis, pneumonitis, and tonsillitis, to name a few. When a kidney infection results in kidney damage, it may be indistinguishable from a non-infectious infection[6].

According to the authors Sidorov S.S., Petrova M.M. (2018), there are several mechanisms through which viral syndromes can lead to glomerulopathy. Direct infection of glomerular cells can cause cytopathic damage. Like any filterable blood-borne substance, viral particles (5–300 nm in diameter) can engulf the glomerular filtration apparatus, resulting in the formation of immune complexes (IC) in situ. Viruses can be an antigenic stimulus to the immune system, resulting in autoimmunity against

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cross-reactive glomerular cell epitopes [4]. Alternatively, direct infection may modify either the tissue antigen or the cellular immune response, causing autoimmunity [5]. Viral infections of the kidney can lead to chronic nephropathy through a variety of mechanisms, including reactivation of latent virus in glomerular cells, leading to recurrent lesions of kidney cells.

Establishment of virus-associated glomerulopathy requires diagnostic evidence of viral infection as well as clinical or pathologic evidence of renal injury, obtained either by histopathology, viral culture, or evidence of viral replication by polymerase chain reaction (PCR). This is not an easy task and has not been performed well in many case reports or cohort studies of kidney injury in viral syndromes. Albuminuria and erythrocyturia occur nonspecifically in many febrile illnesses and do not in themselves indicate glomerular damage. Viruria or inclusion cells in the urine may be either a cause or consequence of glomerular damage, or may simply reflect glomerular uptake during viremia. Some viruses are commensal in the kidney and can be released harmlessly. Although polyoma viruses (BK and JC viruses) are known to infect tubular and, less commonly, glomerular epithelial cells in the kidney and cause interstitial nephritis and, less commonly, crescentic glomerulonephritis (GN) in transplanted kidneys, no cases of these diseases have been reported.

If a particular virus does cause glomerulopathy, viruria may be observed prodrome, during illness, during convalescence, or indefinitely. In a biopsy, viral infection can be determined by identifying inclusion-bearing cells, detecting viral replication using PCR (for DNA viruses), or reverse transcription (RT)-PCR (for RNA viruses), or culturing virus from unfixed samples. Cellular inclusions are nonspecific , and similar bodies can appear in urine during non-viral infections and in healthy individuals. Appropriate controls should be used when immunostaining for antiviral antibodies, and tests may be falsely negative if epitopes are hidden by endogenous antibody binding. Serological antibody data can also be misleading. In systemic autoimmune diseases, nonspecific immune activation may lead to an increase in antiviral antibody titers.Screening for total immunoglobulin titers can help in this regard.In contrast, absorption of pathogenic antiviral antibodies into the glomeruli may reduce the level of detectable antibodies in the bloodstream, leading to a false-negative test result. Therefore, measurement of antibody titer alone should not be considered as evidence of the presence or absence of virus-associated glomerulopathy.

The purpose of this review is to present the available data on known viral pathogens that may be associated with the development or exacerbation of glomerulopathies in the native kidney, with an emphasis on data from children. Pediatric cases of human immunodeficiency virus (HIV) nephropathy will not be included as they have become rare in the era of highly active antiretroviral therapy and have recently been reviewed [7]. A detailed review of viral nephropathies in patients with a transplanted kidney has already been published in the journal Pediatric Nephrology [8]. However, systematic studies of viral infection in children or adults with glomerular diseases comparable to ongoing microbiome analyzes are still lacking in the literature. Until such an approach is developed, the importance of identifying viral infections for the treatment of glomerular diseases will remain uncertain.

Numerous viruses are causally associated with the development of acute immune complex glomerulonephritis. Adenovirus has been cultured in children with pneumonia and ICGN [9] (currently classified as C3 glomerulopathy [10]). Varicella zoster virus (VZV) was the first nephritis-associated virus, identified by Eduard Heinrich Henoch in 1884 [3]. Patients develop proteinuria and microscopic or gross hematuria either before or during exanthema [11]. VZV has been associated with rapidly progressive glomerulonephritis (RPGN) [10]. Case series of children with CMV-[12] and parvovirus-associated GN (also known as post-infectious/post-streptococcal glomerulonephritis, PIGN [13]), as well as case reports of Epstein-Barr virus (EBV)-influenza, have also been published. GN associated

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with mumps, dengue, echovirus, coxsackievirus, hepatitis A virus (HAV) and hepatitis B virus (HBV) [14].

Histologic changes typically resemble poststreptococcal GN but may be accompanied by signs of viral infection. In VZV, vesicular lesions of the renal capsule or intranuclear inclusions are identified both in the walls of the glomerular capillaries and in the mesangium. VZV antigens were detected in the mesangium by immunostaining, and viral particles were isolated from kidney tissue. Obtained from kidney biopsies of EBV-associated ICGN contained Paul-Bunnell (antiheterophile) immunoglobulin M (IgM) antibodies [15]. During measles infection, characteristic giant cells were found in the mucous membrane of the bladder [12], a viral antigen was found in the cytoplasm of parietal glomerular epithelial cells, and binucleate cells were found in the urine. Coxsackievirus B4 has been isolated from urine [13] and HBV surface antigen (HBsAg) has been detected in glomeruli by immunostaining [14] .

Outcomes vary, but some adults with viral ICGN develop azotemia, oliguria, edema, and hypertension [10]. Steroids were found to be a safe and effective treatment in a 14-year-old boy with mononucleosis and RPGN [15]. Two out of three cases of mumps-associated GN in the United States are fatal. However, most patients respond spontaneously to conservative treatment.

Cytomegalic inclusion disease (CID) is estimated to occur in 1–2% of all live births. The diagnosis of disseminated CMV infection is made by cytological examination of urine, in which “owl-like” intracytoplasmic inclusions can be detected in exfoliated tubular epithelial cells. Two cases of diffuse proliferative GN have been reported. Additional case reports of CID with glomerular inclusions have also shown focal segmental and global necrotizing GN and diffuse mesangial sclerosis, implicating CMV infection as one of the causes of congenital NS.

Similar to the responses observed with antiretroviral therapy for HIV nephropathy [16-18], remission of NS in cases of CMV infection has been achieved with ganciclovir. Although follow-up in the CMV nephropathy studies was not long-term, relapses were not reported. Some adults with CMV and collapsing glomerulopathy developed progressive renal failure and end-stage renal disease, but in other cases recovery of renal function was observed with ganciclovir and steroids. The prognosis for parvovirus infection and CG varies from spontaneous remission after resolution of the infection to progression of FSGS and chronic kidney disease. There is no evidence to suggest that relapses of NS caused by viral infection respond more quickly or slowly than relapses caused by other triggers, or that any association of the onset of NS with specific infections will have any effect on steroid sensitivity or dependence.

Conclusion

Available data do not support separate treatment strategies for idiopathic and virus-associated glomerulopathies, with the exception of HIV infection, viral hepatitis, and CMV infections, for which antiviral drugs may be effective. Case reports of spontaneous recovery challenge the notion that all glomerular lesions require immunomodulatory treatment regardless of viral infection status. Some common viruses associated with glomerulopathies, such as chickenpox, influenza, and HBV, can be prevented through vaccination. To report future cases of virus-associated GN, investigators should include renal biopsy with ultrastructural analysis, assessment of viral infection of the renal tissue, and the temporal relationship between infection, specific antibody response, and disease progression. Increasing antibody titers, in situ hybridization, and blood and urine cultures can be confirmatory but may simply identify chronic infection or carriage. Additional prospective studies similar to the Nefrovir study should be performed to explore the role of new viruses. It is clear that viral syndromes act as a trigger for the onset and recurrence of NS, but in this case it is important to distinguish between primary and secondary forms of glomerulopathy.

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