

Viral-associated glomerulopathies in children

Scott E. Wenderfer

Received: 15 September 2014 / Revised: 11 January 2015 / Accepted: 19 January 2015 / Published online: 10 March 2015
© IPNA 2015

Abstract Viral infections associate temporally with the onset of many glomerular diseases, particularly in children. In other cases of glomerulonephritis, when infection is clinically silent, viral syndromes can still be implicated as a trigger. However, strong evidence for viral causality in most glomerular disease is still lacking. While numerous case reports in children document the occurrence of specific forms of glomerular disease after seroconversion to a wide range of viruses, relatively few reports provide pathologic evidence of viral infection associated with glomerular lesions on kidney biopsy. Strong associations between hepatitis viruses and glomerular injury have been acknowledged in adults, but hepatitis C virus appears not to be an etiology in children. In the context of treating glomerular diseases, when diagnosed, the treatment of hepatitis B virus, cytomegalovirus and human immunodeficiency virus in children with membranoproliferative, membranous and collapsing glomerulopathy plays an important role. Otherwise, there is no evidence suggesting that the identification of a viral infection in a child with glomerulopathy should change the management of the infection or the glomerulonephritis. Therefore, additional research into this topic is very much needed.

Keywords Virus · Glomerulonephritis · Nephropathy · Pediatrics · Pathology

Electronic supplementary material The online version of this article (doi:10.1007/s00467-015-3057-y) contains supplementary material, which is available to authorized users.

S. E. Wenderfer (✉)
Renal Section, Department of Pediatrics, Baylor College of
Medicine, Texas Children's Hospital, Houston, TX, USA
e-mail: wenderfe@bcm.edu

Introduction

Viral syndromes are often implicated as probable triggers for 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 that study, 32 children with NS were followed over two winters, with repeated cultures and daily urinalyses. Within 10 days of many of the relapses, infections with respiratory syncytial virus (RSV), influenza, parainfluenza, varicella or adenovirus were detected. 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 single strain of virus has been definitively shown to cause any specific renal pathology, several glomerular diseases are linked to infection or host antiviral responses. Most of these association studies are dated and involve small numbers of patients. A re-examination of these associations is warranted now that newer molecular diagnostics are available, many glomerular disease classifications have been revised and vaccines have changed the patterns of viral infection. Ultimately, pediatric nephrologists may find that outcomes of viral-associated glomerulopathies differ significantly from those of the truly idiopathic forms.

According to the International Committee on Taxonomy of Viruses (<http://ictvonline.org>), there are seven orders, 103 families, 455 genera and more than 2,800 species of viruses. Although only a fraction of these species are known to infect humans, the number of human viral pathogens continues to increase (Table 1). Viruses in general are polytropic, affecting several tissues or organ systems. Kidney cells often are infected during viral illnesses but appear to be unusually resistant to injury compared to other organs and tissues. Both viruria and viremia are often measurable during viral syndromes. Human kidney cells have commonly been used to culture several

Table 1 Taxonomy of viruses infectious to humans

Family	Genus	Species	Glomerulonephritis? ^a
dsDNA viruses			
Adenoviridae	<i>Mastadenovirus</i>	Human adenovirus A, B, C, D, E, F, G	Y
Herpesviridae	<i>Simplexvirus</i>	Human herpesvirus 1,2 (HSV)	Y
	<i>Varicellovirus</i>	Human herpesvirus 3 (VZV)	Y
	<i>Lymphocryptovirus</i>	Human herpesvirus 4 (EBV)	Y
	<i>Cytomegalovirus</i>	Human herpesvirus 5 (CMV)	Y
	<i>Roseolovirus</i>	Human herpesvirus 6A, 6B, 7 (HHV)	N
Papillomaviridae	<i>Mupapillomavirus</i>	Human papilloma virus 1	N
	<i>Alphapapillomavirus</i>	Human papilloma virus 2, 6, 11, 16, 18	N
Polyomaviridae	<i>Polyomavirus</i>	BK, JC, Simian virus 40	N
Poxviridae	<i>Molluscipoxvirus</i>	Molluscum contagiosum virus	N
	<i>Orthopoxvirus</i>	Cowpox, Vaccinia, Variola virus	Y
ssDNA viruses			
Anelloviridae	<i>Alphatorquevirus</i>	Torque teno virus (TTV)	N
Parvoviridae	<i>Dependovirus</i>	Adeno-associated virus-1, 2, 3, 4, 5	N
	<i>Erythrovirus</i>	Human parvovirus B19	Y
dsRNA viruses			
Reoviridae	<i>Rotavirus</i>	Rotavirus A, B, C, D, E	N
Negative-sense ssRNA viruses			
Arenaviridae	<i>Arenavirus</i>	Lymphocytic choriomeningitis virus (LCMV)	N
	<i>Deltavirus</i>	Hepatitis D virus (HDV)	N
Bunyaviridae	<i>Bunyavirus</i>	Bunyamwera virus	N
	<i>Hantavirus</i>	Hantaan virus	Y
	<i>Nairovirus</i>	Dugbe virus	N
	<i>Phlebovirus</i>	Rift Valley fever virus	N
Filoviridae	<i>Ebolavirus</i>	Ebola virus	N
	<i>Marburgvirus</i>	Marburg virus	N
Orthomyxoviridae	<i>Influenzavirus A</i>	Influenza A virus	Y
	<i>Influenzavirus B</i>	Influenza B virus	Y
	<i>Influenzavirus C</i>	Influenza C virus	N
Paramyxoviridae	<i>Metapneumovirus</i>	Human metapneumovirus	N
	<i>Morbillivirus</i>	Measles virus	Y
	<i>Pneumovirus</i>	Respiratory syncytial virus (RSV)	N
	<i>Respirovirus</i>	Parainfluenza 1, 3, Sendai virus	N
	<i>Rubulavirus</i>	Mumps, Parainfluenza virus 2, 4	Y
Rhabdoviridae	<i>Lyssavirus</i>	Rabies virus	Y
	<i>Vesiculovirus</i>	Vesicular stomatitis virus (VSV)	N
Positive-sense ssRNA Viruses			
Astroviridae	<i>Astrovirus</i>	Astrovirus 1	N
Caliciviridae	<i>Norovirus</i>	Norwalk virus	N
	<i>Sapovirus</i>	Sapporo virus	N
Coronaviridae	<i>Alphacoronavirus</i>	Coronavirus 229E, NL63	N
	<i>Betacoronavirus</i>	Coronavirus HKU1 (SARS)	Y
	<i>Torovirus</i>	Torovirus	N
Flaviviridae	<i>Flavivirus</i>	Dengue, St. Louis, West Nile, Yellow fever	Y
	<i>Hepacivirus</i>	Hepatitis C virus (HCV)	Y

Table 1 (continued)

Family	Genus	Species	Glomerulonephritis? ^a
Hepeviridae	<i>Hepevirus</i>	Hepatitis E virus (HEV)	N
Picomaviridae	<i>Aphthovirus</i>	Foot-and-mouth disease virus O	N
	<i>Cardiovirus</i>	Encephalomyocarditis virus	N
	<i>Enterovirus</i>	Coxsackie A, B, Echovirus 6, Poliovirus	Y
		Rhinovirus A, B, C	N
	<i>Hepatovirus</i>	Hepatitis A virus (HAV)	Y
	<i>Parechovirus</i>	Human parechovirus	N
Togaviridae	<i>Alphavirus</i>	Barmah Forest (BFV), Ross River virus (RRV)	Y
	<i>Rubivirus</i>	Rubella virus	Y
DNA and RNA reverse transcribing viruses			
Hepadnaviridae	<i>Orthohepadnavirus</i>	Hepatitis B virus (HBV)	Y
Retroviridae	<i>Lentivirus</i>	Human immunodeficiency virus 1, 2 (HIV)	Y
	<i>Deltaretrovirus</i>	Human T-lymphotropic virus (HTLV)	N

ds double-stranded, *ss* single-stranded

^a Virus has been associated (yes, Y) or not (no, N) with glomerular disease in native kidneys

viruses in the laboratory, including adenovirus, cytomegalovirus (CMV), Coxsackievirus, measles and varicella viruses [3]. The kidneys rarely bear the brunt of infection, either from cytotoxic effects or the host antiviral responses, which is in contrast to viral arthritis, hepatitis, meningitis, otitis, pharyngitis, pericarditis, pneumonitis and tonsillitis, to name a few. When kidney infection leads to kidney injury, it may be indistinguishable from that of non-infectious etiologies.

There are several mechanisms by which viral syndromes can lead to glomerulopathy. Direct infection of glomerular cells can cause cytopathic injury. Like any filterable blood-borne substance, viral particles (diameter 5–300 nm) can become trapped in the glomerular filtration apparatus, leading to in situ immune complex (IC) formation. Viruses can be an antigenic stimulus for the immune system, leading to autoimmunity against cross-reactive glomerular cell epitopes [4]. Alternatively, direct infection may modify either a tissue antigen or a cellular immune response to evoke autoimmunity [5]. Viral infections of the kidney could lead to chronic nephropathy by a variety of mechanisms, including reactivation of latent virus in glomerular cells resulting in recurrent insults to kidney cells.

Establishing a viral associated-glomerulopathy requires diagnostic evidence of viral infection, along with clinical or pathologic evidence of kidney injury, either by histopathology, viral culture or evidence of viral replication by polymerase chain reaction (PCR). This is not a simple task and has not been performed adequately in many of the case reports or cohort studies of kidney involvement during viral syndromes. Albuminuria and erythrocyturia occur non-specifically in many febrile diseases and do not alone establish glomerular injury. Viruria or inclusion-bearing cells in the urine can be either a cause or an effect of glomerular injury, or may simply reflect

glomerular trapping during viremia. Some viruses are commensal in the kidney and may be shed harmlessly. While polyoma viruses (BK and JC viruses) are known to infect tubular and, rarely, glomerular epithelial cells in the kidney, and to cause interstitial nephritis and, rarely, crescentic glomerulonephritis (GN) in transplanted kidneys, there are no reported cases of these viruses infecting glomerular cells or causing glomerulopathy in native kidneys, even in immunosuppressed patients.

If a particular virus does actually cause glomerulopathy, the viruria could occur in the prodromal period, during the illness, in convalescence or indefinitely. On biopsy, viral infection can be determined by identifying inclusion-bearing cells, detecting viral replication by PCR (for DNA viruses, see Table 1) or reverse transcription (RT)-PCR (for RNA viruses) or culturing virus from unfixed specimens. Cellular inclusions are non-specific, and similar bodies can appear in the urine during non-viral infections and in healthy individuals. Proper controls should be used when performing immunostaining for antiviral antibodies, and tests can be falsely negative if epitopes are hidden by endogenous antibody binding. Serological antibody data can also be misleading. In systemic autoimmune diseases, non-specific immune activation may lead to elevations of antiviral antibody titers [6]. Screening total immunoglobulin titers can be helpful in this regard. In contrast, absorption of pathogenic antiviral antibodies in glomeruli may deplete levels of detectable antibody in the circulation, leading to a falsely negative test. Therefore, measuring antibody titers alone should not be taken as proof for the presence or absence of a viral-associated glomerulopathy.

The goal of this review is to present the available evidence for known viral pathogens that may relate to the development or exacerbation of glomerulopathies in native kidneys

(summarized in Table 1), with an emphasis on data available from pediatric subjects. Pediatric cases of human immunodeficiency virus (HIV)-nephropathy will not be included, as these have become rare in the era of highly active antiretroviral therapy and have recently been reviewed [7]. A comprehensive review has already been published in *Pediatric Nephrology* on viral nephropathies in immunosuppressed kidney transplant patients [8]. However, systematic investigations of viral infection in children or adults with glomerular diseases, comparable to the analyses of the microbiome that are being pursued, are still lacking in the literature. Until such an approach can be devised, the importance of identifying viral infections in managing glomerular disease will remain uncertain.

Acute immune complex GN

Numerous viruses have been causally linked to development of an acute immune complex glomerulonephritis (ICGN; Table 2). Adenovirus has been cultured in children with pneumonia and ICGN [9] (currently classified as C3 glomerulopathy [10]). Varicella zoster virus (VZV) was the first virus to be associated with nephritis, identified by Eduard Heinrich Henoch in 1884 [3]. Affected individuals develop proteinuria and microscopic or gross hematuria either before or during the exanthema [11]. VZV has been associated with rapidly progressive glomerulonephritis (RPGN) [10]. Case series have also been published of children with CMV- [12] and parvovirus-associated GN (also known as postinfectious/poststreptococcal glomerulonephritis, PIGN [13]), as have case reports, for Epstein–Barr virus (EBV)-, influenza-, mumps-, Dengue-, echovirus-, Coxsackie-, hepatitis A virus (HAV)- and hepatitis B virus (HBV)-associated GN (Table 2) [14].

Histologic changes tend to resemble post-streptococcal GN, but they can be accompanied by signs of viral infection.

Table 2 Viruses associated with endocapillary glomerulonephritis

Virus	Cases ^a
Adenovirus	2 CS
Varicella zoster virus (VZV)	6 CR
Epstein–Barr virus (BV)	2 CR
Cytomegalovirus (CMV)	1 CS
Parvovirus	1 CS
Influenza virus	2 CR
Mumps virus	6 CR
Dengue virus	1 CR
Echovirus	1 CS
Coxsackievirus	1 CS
Hepatitis A virus (HAV)	3 CS
Hepatitis B virus (HBV)	1 CS
Human immunodeficiency virus (HIV)	2 CS

^a Numbers of care reports (CR) or case series (CS)

In VZV, vesicular lesions of the renal capsule or intranuclear inclusions in both glomerular capillary walls and the mesangium have been identified. VZV antigens have been detected in the mesangium by immunostaining, and virus particles have been cultured from kidney tissue. Eluates obtained from kidney biopsies from EBV-associated ICGN have contained Paul–Bunnell (anti-heterophile) immunoglobulin M (IgM) antibodies [15]. With measles infection, characteristic giant cells have been found in the bladder mucosa [3], viral antigen has been detected in the cytoplasm of parietal glomerular epithelial cells and binucleated cells have been detected in the urine. Coxsackie virus B4 has been cultured from the urine [3], and the surface antigen of HBV (HBsAg) has been detected in glomeruli by immunostaining [14].

Outcomes vary, but some adults with viral-associated ICGN progress to become azotemic, oliguric, edematous and hypertensive [10]. Steroids were a safe and effective therapy in one 14-year-old boy with mononucleosis and RPGN [16]. Two of three cases of mumps-associated GN in the USA were fatal [17]. However, the majority of patients respond spontaneously after conservative management.

Mesangioproliferative GN

Many published cases of viral-associated GN have not shown endocapillary proliferation on biopsy, but rather mesangial proliferation (mesGN). In a case series of pediatric patients with HBV-associated glomerulopathies, two of the 24 children developed mesGN [18]. Acute GN preceded the exanthema by 7 days in a case of VZV-associated GN [19], whereas exanthema preceded urinary findings by 4 days in a case of measles-associated GN [20]. Case reports have also been published with EBV, CMV, mumps, the Ross River togavirus and hepatitis A (Table 3) [10].

Table 3 Viruses associated with mesangioproliferative glomerulonephritis

Virus	Cases ^a
Adenovirus	1 CS
Varicella virus	1 CR
Epstein–Barr virus (EBV)	2 CR
Cytomegalovirus (CMV)	1 CR
Parvovirus	1 CS
Influenza virus	1 CS
Measles virus	1 CR
Mumps virus	1 CR
Toga virus	1 CR
Hepatitis A virus (HAV)	1 CR
Hepatitis B virus (HBV)	1 CS
Human immunodeficiency virus (HIV)	2 CS

^a Numbers of case reports (CR) or case series (CS)

Diagnosis of viral-associated mesGN has been based on specific testing. Eluates from kidney biopsy have tested positive for anti-heterophile antibodies in EBV infection [15]. Intracytoplasmic inclusions have been detected in glomeruli of patients with CMV [21]. Viral antigen has been detected in the mesangium by immunostaining in CMV, measles [20] and HBV infection, and mumps virus has been detected by PCR [22].

Viral-associated mesGN has a good prognosis. In one study, therapy of CMV-associated GN with gancyclovir was associated with full remission [23]. Other cases appear to resolve with clearance of the viral infection.

Henoch–Schönlein purpura and IgA nephropathy

Several viruses have been considered to be etiologic agents in the development of Henoch–Schönlein purpura (HSP) or IgA nephropathy (IgAN) (Table 4), but none has been reproducibly identified in large cohorts. Adenovirus and CMV infections of the kidney have been implicated in the past, but direct connections have proven to be false [24]. However, specific viral infections could account for specific subsets of patients. In one study, the titers of herpes simplex virus (HSV)-specific—but not EBV-specific—antibodies were significantly higher in the 54 German patients with IgAN than in the controls [25]. HSV-2 antigens were detected in the mesangium of two patients with IgAN [25]. In a retrospective review of 88 children with HSP, two had VZV, one had measles and one had rubella infection 2–5 weeks prior to onset of nephritis [26]. Renal involvement was limited to mild transient proteinuria in a third case of VZV-associated HSP [27].

Cytomegalovirus has been detected in mesangial cells, parietal epithelial cells and tubular epithelial cells by in situ hybridization and confirmed by PCR [28]. Mumps viral RNA has been detected on biopsy by RT-PCR [22]. Tubuloreticular inclusions, which are thought to represent

interferon responses, have commonly been identified in glomerular endothelium in hepatitis A-associated IgAN [29].

Prognosis of viral-associated HSP has been mixed. A 9-year-old Japanese boy with a fatal case of HSP was found to have disseminated CMV disease involving the kidneys [28]; his vasculitis was refractory to therapy to remove the IgA immune complexes, including methylprednisolone, urokinase and double filtration plasmapheresis. In contrast, a 5-year-old patient whose HSP nephritis onset was temporally associated with parvovirus infection responded well to standard therapy [30]. Outcomes in cases of viral-associated IgAN have not been distinguished from those of non-infectious IgAN.

Membranoproliferative GN

Unlike in adults, membranoproliferative glomerulonephritis (MPGN) has been associated with viral infections in only a limited number of children (Table 5). The most commonly reported virus associated with pediatric MPGN is HBV, although it is only rarely encountered [31]. Despite the routine testing of idiopathic MPGN patients for hepatitis viruses in many pediatric centers, only a few cases have been published [14, 18, 32]. The largest case series include 12 Polish [14] and seven Turkish children [32], respectively, with positive antibody titers and antigenemia. Pediatric cases of parvovirus B19- [13], influenza- [10] and HAV-associated MPGN have been reported (Table 5).

HCV has been implicated in many autoimmune diseases in adults: cryoglobulinemia, MPGN, membranous nephropathy (MN), systemic lupus erythematosus, antiphospholipid antibody syndrome, Sjogren’s syndrome, autoimmune hemolytic anemia, polyarteritis nodosa and fibromyalgia. Chronic active infection leads to cryoglobulinemia in 40–60 % of adults, and the prevalence increases with the duration of the hepatitis. The virus induces a lymphoproliferative disorder of antibody-producing cells which drives the IC disease and results in a systemic inflammatory syndrome. The cryoglobulinemia presents with Meltzer’s triad of purpura, arthralgias and weakness. Hypocomplementemia is common, with a more predominant depletion of C4 due to activation of the classical pathway. Among adult patients with cryoglobulinemia, 33 % have kidney involvement, many with MPGN [33]. Despite the well-established connection between HCV, cryoglobulins

Table 4 Viruses associated with Henoch–Schönlein purpura nephritis/immunoglobulin A nephropathy

Virus	Cases ^a
Herpes simplex virus (HSV)	1 CS
Varicella zoster virus (VZV)	1 CR, 1 CS
Cytomegalovirus (CMV)	1 CR
Parvovirus	1 CR
Measles virus	1 CR
Mumps virus	1 CR
Rubella virus	1 CR
Hepatitis B virus (HBV)	1 CR
Human immunodeficiency virus (HIV)	1 CS

^a Numbers of care reports (CR) or case series (CS)

Table 5 Viruses associated with membranoproliferative glomerulonephritis

Virus	Cases ^a
Parvovirus	1 CS
Influenza virus	2 CR
Hepatitis A virus (HAV)	1 CR
Hepatitis B virus (HBV)	1 CR, 4 CS
Hepatitis C virus (HCV)	2 CR

^a Numbers of care reports (CR) or case series (CS)

and glomerular disease in adults, there has been a paucity of reported cases in children [31], possibly because it takes decades for chronic infections to induce the production of circulating cryoglobulins at levels sufficiently high to trigger tissue injury. Two pediatric cases in Japan were reported without cryoglobulins, with one patient 2 years into interferon therapy (Table 5).

As opposed to patients with idiopathic MPGN, the biopsies of HCV-infected MPGN patients had a glomerular basement membrane with a double-contour appearance due to the interposition of leukocytes, rather than mesangial cells. HCV antigens have been detected in glomeruli by immunostaining, and HCV-specific antibodies have been eluted from patient glomeruli. HBsAg have been detected in glomeruli in some patients [14] but not all [32].

Kidney injury in viral MPGN responds to antiviral treatment, and many options are now available for HCV [34]. The KDIGO (Kidney Disease: Improving Global Outcomes) guidelines suggest combined antiviral treatment for HCV-associated MPGN using pegylated interferon and ribavirin, titrated according to patient tolerance and level of renal function [35]. For patients at CKD stages 3–5 and with GN who are not yet on dialysis, dose-adjusted pegylated interferon should be used as monotherapy. The use of plasmapheresis, cyclophosphamide or rituximab is reserved for HCV-associated cryoglobulinemia and is unlikely to be effective in children who lack this disease manifestation. Similarly, antiviral therapy with interferon alpha or nucleoside analogs is recommended for HBV infection and MPGN [35]. At the present time, the numbers are too small to predict prognosis of viral-associated MPGN, but one child with influenza and MPGN had acute kidney injury that partially recovered at 8 months, and the others went into complete remission after only 6 months.

Thrombotic microangiopathy

Whereas thrombotic microangiopathies (TMA) due to Shiga toxin- or neuraminidase-producing bacteria are clearly infectious in etiology, the role of viral infections in other forms of TMA remains unclear. Adenovirus and enterovirus infections have been temporally associated with some cases of diarrhea-positive HUS [2], as have VZV and EBV infections (Table 6). Thrombotic thrombocytopenic purpura (TTP) with renal

involvement has been reported in association with H1N1 influenza. CMV and human herpesvirus 6 (HHV6) infection or reactivation have been reported to cause endothelial dysfunction and possibly TMA [36]. There has been no evidence of viral particles in the kidneys of any of these cases, nor was immunostaining for viral antigens attempted.

In that study, the case of VZV-associated TMA was fatal, but the case of EBV-associated TMA responded to steroids. The case of TTP and nephritis associated with influenza responded to pheresis. There is no knowledge of efficacy or safety of eculizumab in viral-associated cases of TMA.

Renal vasculitis

Although not common, cases of children with viral-associated renal vasculitis have been reported for EBV [37], parvovirus [13] and yellow fever [3] (Table 7). The onset of microscopic polyangiitis (MPA) has also been associated with a togavirus endemic to Australia [the Ross River virus (RRV)] in four patients [38]. Polyarteritis nodosa is a known complication of active hepatitis B infection in children [39]. There are also case reports of crescentic GN with antineutrophil cytoplasmic antibody-associated vasculitis that began 3 weeks after the patients received inactivated influenza vaccination. Therefore, viral infection may not be required, but rather immune activation by viral antigens may be more important. Although cases of Goodpasture syndrome associated with rising influenza A titers have been noted in adults, there have been no similar cases seen in children. None of these cases had any evidence of viral particles in the biopsy, nor was immunostaining for viral antigens attempted.

Kidney biopsy in viral-associated vasculitis typically displays a pauci-immune GN with necrotizing lesions [13]. EBV antigens have been detected in the glomerular capillary loops by in situ hybridization [37]. Yellow fever virus also causes congestion, hemorrhage, intranuclear inclusions and desquamation of parietal epithelial cells [3]. HBsAg has been detected in glomeruli by immunostaining [14]. Prognosis of viral-associated renal vasculitis appears to vary. Some children have a benign course, while others develop RPGN requiring dialysis but responsive to steroids; and one 11-year-old girl died from treatment-refractory crescentic GN. Overall, outcomes

Table 6 Viruses associated with thrombotic microangiopathy

Virus	Cases ^a
Adenovirus	1 CS
Varicella zoster virus (VZV)	1 CR
Epstein–Barr virus (EBV)	1 CR
Influenza virus	1 CR
Coxsackievirus	1 CS

^a Numbers of care reports (CR) or case series (CS)

Table 7 Viruses associated with necrotizing glomerulonephritis/polyarteritis nodosa

Virus	Cases ^a
Epstein–Barr virus (EBV)	3 CR
Parvovirus	1 CS
Influenza	1 CR
Togavirus	1 CS
Hepatitis B virus (HBV)	1 CS

^a Numbers of care reports (CR) or case series (CS)

Table 8 Viruses associated with minimal change nephrotic syndrome/focal segmental glomerulosclerosis

Virus	Cases ^a
Adenovirus	1 CS
Herpes simplex virus (HSV)	1 CR
Varicella zoster virus (VZV)	2 CR, 1 CS
Epstein Barr virus	1 CR, 1 CS
Cytomegalovirus (CMV)	5 CR, 1 CS
Parvovirus	1 CS
Respiratory syncytial virus (RSV)	1 CS
Influenza virus	2 CS
Parainfluenza virus	1 CS
Hepatitis A virus (HAV)	1 CR
Human immunodeficiency virus (HIV)	3 CS

^a Numbers of care reports (CR) or case series (CS)

reported to date appear to be consistent with idiopathic causes of renal vasculitis.

Minimal change NS and focal segmental glomerulosclerosis

Idiopathic NS has been commonly referred to as an immune-mediated kidney disease, not because of renal inflammation, but rather due to the temporal associations noted with immune activation and the therapeutic responses often seen with immunosuppressive medications. However, there is limited published evidence to support this connection. The results of the Nephrovir study out of France links the onset of NS to infections with EBV, CMV and HHV7 [40]. These investigators used serologic testing of IgM antibodies and quantitative PCR to assess for active infection or viremia. There are four additional pediatric cases of minimal change NS and one case of mesangiolytic and focal segmental glomerulosclerosis (FSGS) that have been temporally associated with infectious mononucleosis and a positive peripheral blood EBV PCR [41] (Table 8). No study has formally tested the role of infections in the onset of NS in patients with known podocyte gene mutations.

There is slightly more data available on the role of viral infections in inducing NS relapses. In a cohort of 32 Canadian children with viral-associated flares of NS, the three most common etiologic agents were RSV, influenza and then parainfluenza [1]. In all, 41 exacerbations and 29 relapses were assessed prospectively, with 70 % found to be associated with respiratory infections and more than half of these identified as RSV, influenza, parainfluenza, varicella or adenovirus by seroconversion, or by a rise in antiviral antibody titers. New varicella infection is a strong trigger of relapse in children and adults, which presents as edema prior to the onset of

rash [42]. There are also case reports of NS relapse after measles or MMR (measles, mumps, rubella) vaccination [43]. HSV-1 infection was associated with new diagnosis of FSGS in a 5-month-old boy with severe viral encephalitis, diagnosed by viral culture and seroconversion (Table 8).

Paradoxically, a temporal association between remission of NS and infection with influenza B was found in a 5-year-old Japanese boy [44]. His remission lasted only until resolution of flu symptoms, at which time the NS relapsed. Other investigations have been able to associate measles infection with remission of idiopathic NS in children [45, 46], and inoculation was tested in two children as a form of therapy. In total, 13 of 21 children reported in the literature had remissions within 1 week of developing exanthema. However, prolonged remissions were not common, and risks were deemed to be too great [46]. These papers were published in the 1940s, and no kidney biopsies were performed. Only relapsing–remitting forms of NS were reported to have responded to measles infection. Therefore, patients with steroid-resistant NS, such as FSGS, were likely among the non-responders. Remission of NS has never been reported with measles vaccination.

Viral glomerulopathies should be considered in cases of secondary FSGS. Collapsing glomerulopathy (CG) is strongly associated with HIV, CMV or parvovirus infection in children [13], and in adults with EBV infection [47]. Minimal change disease or FSGS has been reported and can involve from 1–90 % of glomeruli. Kidney biopsy of HSV glomerulopathy showed mesangial cytomegaly, osmiophilic mesangial deposits and typical intranuclear viral particles that were detected adjacent to regions of segmental sclerosis and podocyte foot process fusion. Segmental mesangial IgM and C3 deposition co-localized to areas of HSV antigen. Occasionally, viral inclusions have been described in either nuclei or cytoplasm of glomerular endothelial cells in CMV-associated disease, and localized to necrotizing lesions [48]. PCR of biopsy tissue has detected CMV [49] and parvovirus B19 DNA [13], along with tubular abnormalities resembling HIV-associated nephropathy. Fixed deposits and positive immunostaining for IgM have been described in HAV infection. Using PCR, simian polyomavirus SV-40 has been identified in biopsy tissue and urinary cells in adults with FSGS [50], suggesting a possible role of occult polyoma virus infection in NS onset or progression in some patients. No sign of direct kidney infection with HSV-1, EBV, HAV, influenza, parainfluenza or RSV has been seen, suggesting that in most cases the infection likely just triggered the glomerulopathy.

Cytomegalic inclusion disease (CID) has been estimated to occur in as many as 1–2 % of all live births. Diagnosis of disseminated CMV infection is made by urine cytology, where “owl-like” intracytoplasmic inclusions can be detected within shed tubular epithelial cells. Two cases of diffuse proliferative GN have been reported. Additional case reports of CID with glomerular inclusions also displayed focal segmental and

global necrotizing GN [48] and diffuse mesangial sclerosis [51], implicating CMV infection as one cause of congenital NS.

Similar to the responses seen with antiretroviral therapy in HIV nephropathy [7], remission of NS in cases of CMV infection has been achieved with gancyclovir. Although the follow-ups in studies of CMV nephropathy have not been long term, relapses have not been reported [51]. Some adults with CMV and collapsing glomerulopathy have developed progressive renal failure and end-stage renal disease, but in other cases renal recovery was seen with gancyclovir and steroids [47]. Prognosis in parvovirus and CG varies from spontaneous remission after the resolution of infection to progression of FSGS and chronic kidney disease. There is no evidence to suggest that relapses of NS due to viral infection respond any faster or slower than relapses induced by other triggers, or that any association of NS onset with particular infections would have any effect on steroid sensitivity or dependence.

Membranous nephropathy

Since the association of HBV and MN was first reported in adults by Combes [52], viral infections have been considered to be an important etiology of secondary MN (Table 9). Although HBV is a less common etiology of MN in children, HBV antigens have been detected in the glomeruli of at least 100 pediatric MN patients on four continents [18, 14, 32]. Prior to routine vaccination, HBV accounted for up to 40–90 % of all pediatric MN cases in these cohorts. Immunosuppression is a risk factor. The clinical presentation of viral-associated MN is similar to idiopathic MN, although hypocomplementemia, cryoglobulinemia or circulating IC have been detected. EBV or CMV infections have been diagnosed by seroconversion and confirmed by peripheral blood PCR.

Glomerular capillary loop staining for HBcAg (hepatitis B core antigen), HBeAg (hepatitis B e antigen), and HBsAg has been observed to vary among patients [14, 18, 32], which suggests IC deposition rather than the direct viral infection of renal tissue. When present, viral antigens have also tended to co-localize with IgG, IgM and C3 in glomerular capillary

loops [14]. CMV infection of the kidney has been reported in MN, by both positive shell vial culture from urine and by tissue PCR.

Prior to the availability of antiviral therapy, the natural history of HBV-associated MN in children was one of slow resolution over several years: the average period of duration of the NS was 5 months and the time to resolution of the proteinuria was 18–20 months. A few patients had persistent asymptomatic proteinuria, but progressive renal failure was rare. The course of disease is unrelated to persistence of HBsAg, but recovery of renal injury is associated with development of antibodies to HBeAg. KDIGO guidelines recommend antiviral therapy for HBV infection and MN with interferon alpha or nucleoside analogs, with dosing adjusted to the degree of renal function [35]. In most reported cases of HBV-associated MN, the NS resolves with clearance of viremia. Corticosteroid treatment has been ineffective in pediatric cohorts of HBV-associated MN and may inadvertently delay seroconversion to anti-HBe status. In refractory cases, cyclosporine has been effective in achieving remission. Gancyclovir has resulted in full remission of proteinuria and hematuria in cases of MN and CMV.

Summary

The available data do not support separate management strategies for idiopathic and viral-associated glomerulopathies, with the exception of HIV, hepatitis virus and CMV infections for which antivirals can be effective. Case reports of spontaneous recovery challenge the notion that all glomerular lesions warrant immunomodulatory treatment regardless of viral infection status. Some common viruses associated with glomerulopathies, such as varicella, influenza and HBV, are preventable by vaccination. For reporting future cases on viral-associated GN, investigators should include renal biopsy with ultrastructural analysis, assessment of viral infection of kidney tissue and temporal association between infection, specific antibody responses and disease course. Increasing antibody titers, *in situ* hybridization and blood and urine cultures can be confirmatory, but may simply identify a chronic infection or carrier state. Additional prospective studies similar to the Nephrovir study should be performed to address the role of emerging viruses. It is clear that viral syndromes act as a trigger for NS onset and relapse, but when this is the case it may be important to discriminate between primary and secondary forms of glomerulopathy.

Acknowledgments The author would like to thank Drs. Michael Braun, Shweta Shah and Xiaoyan Wu for their thoughtful discussions and review of the manuscript. This research was supported by grant no. NIH DK081663 awarded to P.I. Wenderfer.

Table 9 Viruses associated with membranous nephropathy

Virus	Cases ^a
Epstein–Barr virus (EBV)	1 CR, 1 CS
Cytomegalovirus (CMV)	1 CR
Hepatitis B virus (HBV)	2 CR, 12 CS

^a Numbers of care reports (CR) or case series (CS)

Multiple choice questions (Answers are provided following the reference list)

- Which laboratory method alone is MOST indicative of a direct viral infection of the kidney?
 - Elution of viral-specific antibodies from kidney tissue
 - Viral culture of urine
 - Immunostaining for viral antigen in kidney tissue
 - Viral inclusion bodies on electron microscopy of kidney tissue
 - PCR of kidney tissue for viral nucleic acid sequences
- What is the most common histopathology seen in patients with nephropathy associated with hepatitis B virus?
 - Membranous nephropathy
 - Membranoproliferative glomerulonephritis
 - Mesangioproliferative glomerulonephritis
 - Pauci-immune glomerulonephritis
 - Focal segmental glomerulosclerosis
- Based on the only viral surveillance study that tested the proportion of nephrotic syndrome relapses occurring within days of a viral infection (performed in the early 1980s), how commonly do viral syndromes induce relapse?
 - 100 % of the time
 - >50 % of the time
 - only some of the time
 - never
- Besides HIV, there is evidence sufficient to warrant investigation for which viral infection in children with collapsing glomerulopathy?
 - Influenza virus
 - Respiratory syncytial virus
 - Human herpes virus 7
 - Enterovirus
 - Cytomegalovirus
- Immunization with heat killed virus or recombinant viral proteins might trigger glomerulopathies via which mechanism?
 - Reactivation of latent viral infection
 - Lymphoproliferation and cryoglobulinemia
 - Non-specific activation of auto-antibody producing cells
 - Induction of glomerular giant syncytia-like cells
 - Direct toxicity of the adjuvant

References

- MacDonald NE, Wolfish N, McLaine P, Phipps P, Rossier E (1986) Role of respiratory viruses in exacerbations of primary nephrotic syndrome. *J Pediatr* 108:378–382
- Ray CG, Tucker VL, Harris DJ, Cuppage FE, Chin TD (1970) Enteroviruses associated with the hemolytic-uremic syndrome. *Pediatrics* 46:378–388
- Reimann HA (1968) Nephropathy and viroses. *Postgrad Med J* 44: 853–860
- Albert LJ, Inman RD (1999) Molecular mimicry and autoimmunity. *N Engl J Med* 341:2068–2074
- Mackay IR (2000) Science, medicine, and the future: Tolerance and autoimmunity. *BMJ* 321:93–96
- Wilson CB, Dixon FJ, Evans AS, Glassock RJ (1973) Antiviral antibody responses in patients with renal diseases. *Clin Immunol Immunopathol* 2:121–132
- Bhimma R, Purswani MU, Kala U (2013) Kidney disease in children and adolescents with perinatal HIV-1 infection. *J Int AIDS Soc* 16: 18596
- Comoli P, Ginevri F (2012) Monitoring and managing viral infections in pediatric renal transplant recipients. *Pediatr Nephrol* 27:705–717
- Chany C, Lepine P, Lelong M, Le TV, Satge P, Virat J (1958) Severe and fatal pneumonia in infants and young children associated with adenovirus infections. *Am J Hyg* 67:367–378
- Smith MC, Cooke JH, Zimmerman DM, Bird JJ, Feaster BL, Morrison RE, Reimann BE (1979) Asymptomatic glomerulonephritis after nonstreptococcal upper respiratory infections. *Ann Intern Med* 91:697–702
- Yuceoglu AM, Berkovich S, Minkowitz S (1967) Acute glomerulonephritis as a complication of varicella. *JAMA* 202:879–881
- Ozawa T, Stewart JA (1979) Immune-complex glomerulonephritis associated with cytomegalovirus infection. *Am J Clin Pathol* 72: 103–107
- Waldman M, Kopp JB (2007) Parvovirus B19 and the kidney. *Clin J Am Soc Nephrol* 2[Suppl 1]:S47–S56
- Brzosko WJ, Krawczynski K, Nazarewicz T, Morzycka M, Nowoslawski A (1974) Glomerulonephritis associated with hepatitis-B surface antigen immune complexes in children. *Lancet* 2:477–482
- Andres GA, Kano K, Elwood C, Prezyna A, Sepulveda M, Milgrom F (1976) Immune deposit nephritis in infectious mononucleosis. *Int Arch Allergy Appl Immunol* 52:136–144
- Ranganath R, Pandey AR, Pavan M (2011) Crescentic glomerulonephritis and leucocytoclastic vasculitis associated with acute EBV infection. *Nephrology (Carlton)* 16:617
- Hughes WT, Steigman AJ, Delong HF (1966) Some implications of fatal nephritis associated with mumps. *Am J Dis Child* 111:297–301
- Slusarczyk J, Michalak T, Nazarewicz-de Mezer T, Krawczynski K, Nowoslawski A (1980) Membranous glomerulopathy associated with hepatitis B core antigen immune complexes in children. *Am J Pathol* 98:29–43
- Dass R, Singh S, Kumar V, Vaiphei K, Agrawal S, Saeed T, Minz RW (2004) Varicella glomerulonephritis mimicking microscopic polyangiitis. *Rheumatol Int* 24:362–364
- Lin CY, Hsu HC (1983) Measles and acute glomerulonephritis. *Pediatrics* 71:398–401
- Rodriguez-Hitirbe B, Burdman EA, Ophascharensuk, Barsoum R (2000) Glomerular diseases associated with infections. In: Johnson R, Feehally J (eds) *Comprehensive clinical nephrology*, 2nd edn. Mosby, Edinburgh, pp 373–386
- Fujieda M, Kinoshita A, Naruse K, Nakayama T, Moriki T, Wakiguchi H, Kurashige T (2000) Mumps associated with immunoglobulin A nephropathy. *Pediatr Infect Dis J* 19:669–671
- Shiraishi N, Kitamura K, Hayata M, Ogata T, Adachi M, Kajiwara K, Ikeda H, Miyoshi T, Tomita K (2012) Case of anti-glomerular basement membrane antibody-induced glomerulonephritis with cytomegalovirus-induced thrombotic microangiopathy. *Intern Med* 42:e7–e11

24. Kanahara K, Taniguchi Y, Yorioka N, Yamakido M (1992) In situ hybridization analysis of cytomegalovirus and adenovirus DNA in immunoglobulin A nephropathy. *Nephron* 62:166–168
25. Nagy J, Uj M, Szucs G, Trinn C, Burger T (1984) Herpes virus antigens and antibodies in kidney biopsies and sera of IgA glomerulonephritic patients. *Clin Nephrol* 21:259–262
26. Meadow SR, Glasgow EF, White RH, Moncrieff MW, Cameron JS, Ogg CS (1972) Schonlein–Henoch nephritis. *Q J Med* 41:241–258
27. Halle CJ (1979) Henoch–Schonlein purpura after chickenpox. *Arch Dis Child* 54:166
28. Murakami H, Takahashi S, Kawakubo Y, Kinukawa N, Funaki S, Harada K (2008) Adolescent with Henoch–Schonlein purpura glomerulonephritis and intracranial hemorrhage possibly secondary to the reactivation of latent CMV. *Pediatr Int* 50:112–115
29. Zikos D, Grewal KS, Craig K, Cheng JC, Peterson DR, Fisher KA (1995) Nephrotic syndrome and acute renal failure associated with hepatitis A virus infection. *Am J Gastroenterol* 90:295–298
30. Watanabe T, Oda Y (2000) Henoch-Schonlein purpura nephritis associated with human parvovirus B19 infection. *Pediatr Int* 42:94–96
31. Nowicki MJ, Welch TR, Ahmad N, Kuramoto IK, Mendoza EC, Zeldis JB, Baroudy BM, Balistreri WF (1995) Absence of hepatitis B and C viruses in pediatric idiopathic membranoproliferative glomerulonephritis. *Pediatr Nephrol* 9:16–18
32. Ozdamar S, Gucer S, Tinaztepe K (2003) Hepatitis-B virus associated nephropathies: a clinicopathological study in 14 children. *Pediatr Nephrol* 18:23–28
33. Johnson RJ, Gretch DR, Yamabe H, Hart J, Bacchi CE, Hartwell P, Couser WG, Corey L, Wener MH, Alpers CE, Willson R (1993) Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *N Engl J Med* 328:465–470
34. Hellard ME, Doyle JS (2014) Interferon-free hepatitis C treatment: one pill to fit all? *Lancet* 383:491–492
35. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group (2012) KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2:139–274
36. Takatsuka H, Wakae T, Mori A, Okada M, Fujimori Y, Takemoto Y, Okamoto T, Kanamaru A, Kakishita E (2003) Endothelial damage caused by cytomegalovirus and human herpesvirus-6. *Bone Marrow Transplant* 31:475–479
37. Kano K, Yamada Y, Sato Y, Arisaka O, Ono Y, Ueda Y (2005) Glomerulonephritis in a patient with chronic active Epstein–Barr virus infection. *Pediatr Nephrol* 20:89–92
38. Davies DJ, Moran JE, Niall JF, Ryan GB (1982) Segmental necrotizing glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? *Br Med J (Clin Res Ed)* 285:606
39. Gocke DJ, Hsu K, Morgan C, Bombardieri S, Lockshin M, Christian CL (1970) Association between polyarteritis and Australia antigen. *Lancet* 2:1149–1153
40. Dossier C, Sellier-Leclerc A-L, Rousseau A, Michel Y, Gautheret-Dejean A, Englender M, Madhi F, Charbit M, Ulinski T, Simon T, Jacqz-Aigrain E, Deschênes G (2014) Prevalence of herpesviruses at onset of idiopathic nephrotic syndrome. *Pediatr Nephrol* 29:2325–2331
41. Gilboa N, Wong W, Largent JA, Urizar RE (1981) Association of infectious mononucleosis with nephrotic syndrome. *Arch Pathol Lab Med* 105:259–262
42. Lin CY, Hsu HC, Hung HY (1985) Nephrotic syndrome associated with varicella infection. *Pediatrics* 75:1127–1131
43. Kuzemko JA (1972) Measles vaccination and the nephrotic syndrome. *Br Med J* 4:665–666
44. Kimata T, Tsuji S, Kino J, Kitao T, Yamanouchi S, Kaneko K (2013) Close association between proteinuria and regulatory T cells in patients with idiopathic nephrotic syndrome. *Pediatr Nephrol* 28:667–669
45. Meizlik EH, Carpenter AM (1948) Beneficial effect of measles on nephrosis; report of three cases. *Am J Dis Child* 76:83–90
46. Rosenblum AH, Lander HB, Fisher RM (1949) Measles in the nephrotic syndrome. *J Pediatr* 35:574–584
47. Chandra P, Kopp JB (2013) Viruses and collapsing glomerulopathy: a brief critical review. *Clin Kidney J* 6:1–5
48. Cozzutto C, Felici N (1974) Unusual glomerular change in cytomegalic inclusion disease. *Virchows Arch A Pathol Anat Histol* 364:365–369
49. Tomlinson L, Boriskin Y, McPhee I, Holwill S, Rice P (2003) Acute cytomegalovirus infection complicated by collapsing glomerulopathy. *Nephrol Dial Transplant* 18:187–189
50. Li R-M, Branton MH, Tanawattanacharoen S, Falk RA, Jennette JC, Kopp JB (2002) Molecular identification of SV40 infection in human subjects and possible association with kidney disease. *J Am Soc Nephrol* 13:2320–2330
51. Besbas N, Bayrakci US, Kale G, Cengiz AB, Akcoren Z, Akinci D, Kilic I, Bakkaloglu A (2006) Cytomegalovirus-related congenital nephrotic syndrome with diffuse mesangial sclerosis. *Pediatr Nephrol* 21:740–742
52. Combes B, Shorey J, Barrera A, Stastny P, Eigenbrodt EH, Hull AR, Carter NW (1971) Glomerulonephritis with deposition of Australia antigen-antibody complexes in glomerular basement membrane. *Lancet* 2:234–237

Multiple choice answers

1. E
2. A
3. B
4. E
5. C