SECONDARY GLOMERULONEPHRITIDES

This review of the secondary glomerulonephritides outlines presentation clues to assist the primary healthcare worker in making the diagnosis. Glomerulonephritis (GN) due to the following disorders will be described: hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), sickle cell disease (SCD), and systemic lupus erythematosus (SLE). (Ethn Dis. 2003;13(suppl2):S2-125–S2-130)

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HEPATITIS B VIRUS GLOMERULOPATHY

It is estimated that 2 billion individuals worldwide exhibit serological evidence of HBV infection. Of these, 350 million are chronic carriers, and 1 million will die annually from cirrhosis and hepatocellular carcinoma. Infection with HBV is associated with a variety of renal diseases, which occur most commonly in endemic areas, particularly in children. These patients generally test positive for hepatitis B surface antigen (HBsAg) and anti-core antibody, and hepatitis B e antigen (HBeAg) (in patients with membranous nephropathy). Some patients have a history of active hepatitis, but many are asymptomatic, with no, or mild, elevations in serum transaminases. Hepatitis B antigen-antibody complexes have been observed in renal lesions by using immunofluorescence. Both HBV DNA and RNA have been observed in glomerular and tubular cells in these patients.

TYPES OF RENAL DISEASE

Three major forms of renal disease have been described with HBV infection: membranous nephropathy (MN), polyarteritis nodosa (PAN) and membranoproliferative glomerulonephritis (MPGN).

Membranous Nephropathy

The presence of the HbeAg and anti-HBe antibody, has been suggested, but not proven, to be responsible for the formation of pathogenic subepithelial immune deposits. Family members and other household contacts of children with HBV MN are at very high risk for carrying HBV.

Africa

Membranous nephropathy is most common in children in endemic areas. In KwaZulu Natal, South Africa, the prevalence rates of HBsAg in urban, rural, and institutionalized Black children were reported to be 6.3%, 18.5%, and 35.4%, respectively, with the HBV exposure rates, as shown by the presence of any marker of HBV infection, being 19.5%, 65.1%, and 70.1%, respectively. HBV-associated nephropathy is the most common cause of nephrotic syndrome among Black children in KwaZulu Natal; membranous nephropathy is the most common histological type, present in 43% of 306 Black children with nephrotic syndrome; of these, 86.2% were associated with HBV antigens. Membranous nephropathy resolves spontaneously in many children, and is associated with the appearance of free anti-HBe antibodies in the circulation; resolution is relatively uncommon in adults, many of whom have progressive disease. In Cape Town, 46 of 63 children (86.7%) with membranous nephropathy were HBsAg positive and 80% were HBeAg positive; the prevalence of HBsAg in patients with GN other than MN was 10%. In Johannesburg, 14 of 59 Black children (24%) with MN and nephrotic syndrome were all HBsAg- and HBeAg-positive, and 50% had circulating HBV DNA. In Zimbabwe, 8 of 23 children with MN and nephrotic syndrome were all HBsAg- and HBeAg-positive, and 50% had circulating HBV DNA. In Nigeria, where HBV infection is highly endemic, no increase in HBV markers was observed in nephrotic children compared to controls, and none of the biopsies exhibiting MN came from HBsAg-positive patients.

Middle East

The prevalence of HBsAg was 28% in a series of biopsies of 25 children...
Of these [2 billion], 350 million are chronic carriers, and 1 million will die annually from cirrhosis and hepatocellular carcinoma.

with nephrotic syndrome in Saudi Arabia, where there is a high prevalence of HBV infection; of these 7 children (28%), 5 were HBeAg-positive, 3 had MN, 1 had mesangial proliferative GN, and 1 exhibited minimal change disease on renal biopsy.

Asia
In a series of 1250 renal biopsies performed in children in Kobe, Japan, from 1972–1982, 16 of 28 children (57%) were found to have MN in association with HBV infection. In Taiwan, 54 of 463 children (11.7%) with GN also had MN; 96.3% tested positive for HBsAg, and 93% for HBeAg. In Hong Kong, of 311 patients with primary GN, 21% were HBsAg-positive; of this 21%, 64% had MN, 42% had mesangial proliferative GN, and 17% showed IgA nephropathy.

Clinical Presentation of Membranous Nephropathy
In children, MN due to HBV is often asymptomatic, and is detected by routine urine examination and serology, and the other common presentation is a relapsing nephrotic syndrome. There is a strong male predominance in the occurrence of MN associated with HBV. In adults, proteinuria and nephrotic syndrome are the most common presentations, with male predominance being less prominent. Clinical clues for the diagnosis in a child, generally from an endemic area, include the presence of proteinuria, nephrotic syndrome, or hematuria with red cell casts, or any patient with abnormal liver enzymes. Spontaneous regression of nephrotic syndrome in HBV MN has been reported in 30%–60%, and such patients generally remain asymptomatic for 12 months or longer. Seroconversion to anti-HBeAg is associated with remission of proteinuria; progression to renal insufficiency has been reported in patients who do not clear the virus.

Treatment of Membranous Nephropathy
Steroid therapy has been associated with an active viral replication in a prospective controlled study of nephrotic patients with HBV MN. A short course of steroids may be given to patients with active vasculitis to control the inflammatory process. Alpha-interferon (INF-alpha) has been shown to clear HBV DNA and HBeAg, in 30%–50% of patients. At 40 weeks, 52.6% of Black children with HBV-associated nephropathy showed clearance of HBeAg with remission of proteinuria, following treatment with INF-alpha 2b. Combination therapy with INF-alpha and agents such as lamivudine, famciclovir, and adenine arabinoside, needs evaluation; the combination of adenine arabinoside and thymic extract resulted in decreased viral activity, and virtual resolution of proteinuria, in 24 patients with membranous nephropathy.

Polyarteritis Nodosa
Polyarteritis nodosa (PAN), a large vessel vasculitis that can be induced by HBV, in which circulating antigen-antibody complexes may be deposited in the vessels. The vasculitis typically occurs within 4 months after the onset of HBV infection. These patients are typically ANCA-negative, and have HB s and e antigens, and HBV DNA, in the serum.

Treatment of PAN
In a non-randomized prospective trial of 41 patients with HBV-related PAN, treatment with INF-alpha, or adenine arabinoside, along with a 2-week course of corticosteroids and plasmapheresis, demonstrated conversion to HBe antibody positivity in 51% of patients, and 56% showed no serologic evidence of viral replication. At the end of the follow-up period, the vasculitis had subsided in all 33 of the surviving patients, even in those with evidence of persistent HBV infection. Other case reports include successful treatment with INF-alpha and famciclovir.

Membranoproliferative Glomeronephritis
Membranoproliferative glomeronephritis (MPGN) associated with HBV is characterized by the deposition of circulating antigen-antibody complexes in the mesangium and subendothelial spaces. Both HBsAg and HBeAg have been implicated in this condition, but their role is not clear. Some patients with MPGN have mixed cryoglobulinemia; HCV infection may be of pathogenetic importance in this setting.

Renal Transplantation
Renal transplantation is not contraindicated in patients with asymptomatic HBV infection and end stage renal disease. A long-term study of 150 HBsAg-positive renal transplant recipients found that histologic deterioration of the liver was present in 85%, and 30% exhibited cirrhosis; the renal allograft survival rate was significantly reduced, compared to that of uninfected patients. However, there was no overall increase in mortality in these patients, despite the fact that liver disease was the major cause of death among them. The optimal treatment of renal transplant recipients with chronic HBV infection is unclear. Alpha-interferon (INF-alpha), while effective, may precipitate acute rejection. Lamivudine has shown promise in case reports, and its use needs further evaluation.
PREVENTION OF INFECTION: HEPATITIS B VACCINATION

Currently available hepatitis B vaccines are safe, with an efficacy of >90%. Therefore, HBV infection can potentially be eradicated by global vaccination. Vaccination coverage is low in many underdeveloped countries, due to the lack of funding and infrastructure to purchase and deliver the vaccines. Vaccination coverage is also low in many developed countries, due to the misconception that vaccination is only necessary in high-risk groups in non-endemic areas. Pre-vaccination screening is performed to identify individuals who may not require vaccination (eg, adults in endemic areas, patients in high-risk groups); HBsAg and anti-HBs testing is recommended in these individuals.

Indications for Hepatitis B Vaccination

Universal Hepatitis B Vaccination

Universal Hepatitis B vaccination of all newborns can be used as primary prevention to increase overall immunity within a community. Hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) are given simultaneously at 2 different sites, within 12 hours of delivery; 2 additional doses are given at months 1–2 and 6–12; the efficacy of this regimen is 95%. Studies in Thai children and hepatitis B immunoglobulin (HBIG) have equivalent protection; however, these data need to be confirmed.

Catch-up Vaccination

By vaccinating children who were born prior to implementation of universal neonatal vaccination, these children will be immunized before they reach adolescence, when they are at risk of infection via sexual exposure and intravenous drug use.

High-risk Groups

Groups at high-risk of Hepatitis B should receive vaccination and include: sexually active individuals with multiple sex partners; homosexual or bisexual males; household contacts of patients with hepatitis B; intravenous drug users; healthcare workers; patients on chronic hemodialysis; patients requiring blood or blood products repeatedly.

RENAL DISEASE WITH HEPATITIS C VIRUS

The association between chronic hepatitis C virus (HCV) infection and glomerular disease has been established. Three types of renal disease have been recognized: mixed cryoglobulinemia (MC), MPGN, and MN.

Mixed Cryoglobulinemia (MC)

Mixed cryoglobulinemia (MC) is a systemic vasculitis, presenting with non-specific systemic symptoms, such as palpable purpura, hypocomplementemia, and renal disease (hematuria; proteinuria, often in the nephrotic range; renal insufficiency). Renal histology resembles idiopathic MPGN, and also shows the presence of intraluminal thrombi (using light microscopy), and "fingerprint" substructure of dense deposits (using electron microscopy). Features of HCV infection have been noted in 95% of patients with MC. Hepatitis C virus (HCV) antigens were detected along the glomerular capillary walls and mesangium in 8 of 12 patients with HCV-positive MC.

Membranoproliferative Glomerulonephritis

Hepatitis C virus (HCV)-associated MPGN appears to vary by location, being relatively rare in France, the United States, and South Africa, but with increased prevalence in Japan (6 of 10 cases of MPGN with HCV RNA), and Egypt.

Membranous Nephropathy

Membranous nephropathy (MN) has also been associated with chronic HCV infection. Unlike MC or MPGN, serum complement levels tend to be normal, and neither cryoglobulins nor rheumatoid factors are present in HCV-associated MN.

Diagnosis of MC, MPGN, and MN

It has been suggested that all patients with MC, MPGN, and, possibly, MN, should be evaluated serologically for possible underlying HCV infection. Most patients exhibit evidence of liver disease (an elevated level of transaminases); however, the level of transaminases are normal in some patients, and a history of acute hepatitis is often absent.

Treatment of MC, MPGN, and MN

Patients with HCV-induced renal disease should receive a combination of INF-alpha and ribavirin; however, ribavirin is not recommended if the creatinine clearance is <50 mL/minute, in which instance INF-alpha, alone, is utilized. Alpha-interferon (INF-alpha) given to 14 patients with MPGN resulted in a clearing of HCV RNA, and reduction in proteinuria, in approximately 50% of patients. In a randomized prospective trial of 53 patients with MC, treated either with INF-alpha or conventional therapy, HCV RNA decreased to undetectable levels, and patients in the INF-alpha group demonstrated improvement in cutaneous vasculitis, cryoglobulin titers, and plasma creatinine.

Patients with severe acute disease (renal failure, neurologic involvement) should initially receive plasmapheresis (to remove cryoglobulins from circulation), corticosteroids (1 g methylprednisolone daily for 3 days, followed by oral prednisone), and cyclophosphamide, to prevent new antibody formation. This regimen improved and stabilized renal function in 55%–87% of patients, though death from vasculitis remained a major problem.
**Hepatitis C Virus and Co-Morbid Conditions**

Patients co-infected with HIV and HCV may be at increased risk for HIV and HCV disease progression, including renal disease. HCV infection may adversely affect the renal function and prognosis of patients with renal disease, due to other causes; for example, nephropathy patients with diabetes and infected with HCV experienced a more rapid decline in renal function, compared to those not infected.

**Human Immunodeficiency Virus**

Patients with HIV infection and renal disease may have acute (ARF) or chronic renal failure (CRF). Acute renal failure (ARF) may be due to acute tubular necrosis (due to volume depletion, infection, or drugs, such as protease inhibitors), rhabdomyolysis, HUS/TTP, acute interstitial nephritis, or lupus-like GN. Chronic renal failure (CRF) may be due to HIV-associated nephropathy (HIVAN), MN, MPGN, or IgA nephropathy. Three types of acute and chronic HIV nephropathies have been linked pathogenically to HIV infection: thrombotic microangiopathies (HUS/TTP), immune complex disease (eg, IgA nephropathy), and HIVAN.

**Thrombotic Microangiopathies**

Thrombotic microangiopathies (HUS/TTP) result from widespread endothelial cell injury due to infection of endothelial cells and features of hemorrhagic uremic syndromes (HUS) include: anemia, signs of hemolysis, and renal insufficiency. Signs of thrombotic thrombocytopenic purpura (TTP) are: thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurological dysfunction, and fever.

**Treatment of HUS/TTP**

Treatments for HUS/TTP include plasmapheresis for TTP, as well as glucocorticoids, aspirin, dipyramidoles, vincristine, immune globulin, and splenectomy.

**Immune Complex Renal Disease**

This form of renal disease occurs more commonly in Caucasian and Asian populations. Many of these diseases (MPGN, MN, post-infectious GN, vasculitis, and cryoglobulinemia) may be associated with infections, or may coexist with HIV infection. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are common in intravenous drug users, and may be transmitted sexually. IgA nephropathy has been identified mainly in Caucasian and Hispanic men with HIV infection. An idiotypic IgA immune response against IgM or IgG antibodies is produced against p24 or gp120 HIV peptides.

**HIV-Associated Nephropathy (HIVAN)**

HIV-associated nephropathy (HIVAN) is the most common renal disease observed in biopsy series of patients with HIV infection and renal disease and presents frequently with nephrotic syndrome. HIV-associated nephropathy (HIVAN) involves all compartments of the kidney. The typical lesion, focal segmental glomerulosclerosis (FSGS), is seen more commonly in adults, frequently with the collapsing variant. Tubular atrophy, microcystic dilatation, and interstitial fibrosis, are frequently noted. A prominent tubulointerstitial infiltrate, most commonly T lymphocytes and macrophages, is a hallmark of the disease. Tubular reticular inclusions in endothelial cells are a common, but nonspecific finding when using electron microscopy in HIVAN biopsies, and are thought to be associated with the action of INF-alpha. Patients present with proteinuria/nephrotic syndrome, renal insufficiency, large echogenic kidneys, and a relatively rapid course to end stage renal disease. Hypertension, edema, and hyperlipidemia are relatively uncommon. Clinically, HIVAN is present mainly in men of African descent with CD4<250. Human immunodeficiency virus (HIV) DNA has been observed in renal cells from biopsies of patients with HIV infection. CXCR4 and CCR5 chemokine receptors are co-receptors for progression of HIV infection. Mutations in these receptors, more common in Caucasians, are associated with decreased susceptibility to HIV infection, improved survival of infected patients, and improved prognosis.

**Treatment for HIVAN**

The following treatment protocol is generally recommended for HIVAN. Cautions are also presented.

1. Immunosuppression with cyclosporine and glucocorticoids
   Cyclosporine has been promising, but is rarely used, due to the fear of systemic immunosuppression. Several reports of patients treated with steroids demonstrated impressive improvement in renal function and proteinuria, however, side effects may prevent its long-term use.

2. Angiotensin-converting enzyme inhibitors
   Angiotensin-converting enzyme inhibitors (ACEIs) decreased proteinuria and improved renal survival, probably by their effect on the renal expression of TGF-beta.

3. Anti-retroviral drugs
   HAART resulted in dramatic remission of signs of renal disease in a patient with biopsy-proven HIVAN; further studies on the role of HAART and ACEIs are needed.

**Sickle Cell Disease**

Hemoglobin S results from the substitution of valine for glutamic acid as...
Class VI: sclerosing lesions
Class V: membranous GN
Class IV: diffuse proliferative GN
Class III: focal segmental proliferative glomerulonephritis (GN)
Class II: mesangial proliferation
Class I: nil or minimal change disease

Table 2. WHO classification of lupus nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>nil or minimal change disease</td>
</tr>
<tr>
<td>II</td>
<td>mesangial proliferation</td>
</tr>
<tr>
<td>III</td>
<td>focal segmental proliferative glomerulonephritis (GN)</td>
</tr>
<tr>
<td>IV</td>
<td>diffuse proliferative GN</td>
</tr>
<tr>
<td>V</td>
<td>membranous GN</td>
</tr>
<tr>
<td>VI</td>
<td>sclerosing lesions</td>
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WHO Classification of Lupus Nephritis

Renal biopsy is essential to determining therapy and prognosis, as the histological class (Table 2) is highly correlated with prognosis, and an aggressive therapeutic approach may reduce mortality from renal failure.

Treatment is not indicated for Class I, or for most cases of Class II lupus nephritis, unless extra-renal manifestations warrant treatment. Glucocorticoids and cyclophosphamide are the mainstays of treatment for patients with Classes III and IV. The treatment regimen currently recommended by many authorities includes:

1. Monthly intravenous cyclophosphamide for 6 months, then every 3 months thereafter for 18–24 months; azathioprine may be substituted in less high-risk patients (eg, Caucasians) after the initial 3–6 months of cyclophosphamide treatment.
2. Steroids—1 mg/kg daily, tapered over 6 months to a maintenance dose of 5–10 mg/day for the duration of treatment.

High dose intravenous steroid pulses are effective for rapidly controlling acute
glomerular inflammation and vasculitis. Mycophenolate mofetil has been used to treat patients with lupus nephritis that is resistant to steroids and cyclophosphamide. The management of Class V is less well-defined, with some authorities advocating steroids and ACEIs, especially for severe nephrotic syndrome. Plasmapheresis has not proven to be of benefit in severe proliferative lupus nephritis in a randomized prospective trial. About 20% of patients develop ESRD, and require dialysis; systemic flares are less frequent, once dialysis is commenced. Recurrence of nephritis and systemic flares is less common after renal transplantation, if transplantation is undertaken when SLE is quiescent.

REFERENCES


