Secondary Membranous Glomerulonephritis

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Abstract

Membranous nephropathy, one of the most common causes of NS in adults, is uncommon in children, representing at most 5% of new cases of nephrotic syndrome in the pediatric age group. Similar to the adult population, the etiology of membranous nephropathy (MN) can be primary (idiopathic) or secondary. Both can be seen in all pediatric age groups from the neonate to the young adult. However, among children younger than 10 years, a secondary diagnosis is usually identified. The identification of the target antigen in primary MN, M type phospholipase A_2 receptor (PLA_2R), and the increasing availability of testing for the PLA_2R antibody has shaped significant research in primary MN over the course of the past decade. In contrast, the literature describing secondary MN in children is limited. Data is extrapolated from studies that originate in the adult population or from pediatric case reports or small case series.

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Secondary causes of membranous nephropathy in children include several broad categories including systemic autoimmune diseases, infections, drugs, and malignancy. Case reports have broadened this list to include several other systemic illnesses that have been associated with MN. The following review will focus on secondary membranous nephropathy, including the prevalence and epidemiology, the histopathology, clinical manifestations, and the specific etiologies with their pathogenesis and prognosis.

Keywords
Secondary membranous · NSAIDs membranous · Autoimmune membranous · Medication membranous · Malignancy membranous · Hepatitis membranous · Membranous lupus

Epidemiology

The prevalence of membranous nephropathy in the pediatric population is difficult to know with certainty, as many patients with steroid sensitive nephrotic syndrome no longer undergo renal biopsy. Based upon historical data and an aggregate of biopsy data from studies in Asia, Europe, the Americas, and the Middle East, the prevalence of membranous nephropathy among *younger* children (<10 years old) with nephrotic syndrome is thought to be about 3%. Among children older than age 12 years, membranous nephropathy may represent as much as 18% of all new diagnoses of nephrotic syndrome (Mubarak et al. 2012; Hogg et al. 1993; Ayalon and Beck 2015). Among younger patients, under 10 years, it is reported that up to 75% of cases are secondary. That percentage drops significantly among adolescents, in large part, due to the increasing incidence of idiopathic PLA_2R-related disease in this age group. Idiopathic membranous nephropathy occurs more commonly in males, in a ratio of just under 1.5:1. Secondary membranous nephropathy occurs more frequently in females, likely due to the increased prevalence of SLE among young women.

Histopathology

The classic histopathology on light microscopy of membranous nephropathy is a diffuse thickening of the glomerular basement membrane (GBM) throughout all glomeruli, in the absence of significant hypercellularity. In more advanced cases, spikes of GBM between immune deposits may appear. Chronic sclerosis and scarring in the glomerulus and significant tubulointerstitial changes occur as the disease progresses. Immunofluorescence microscopy reveals a diffuse granular pattern of IgG and C3 staining along the GBM. Electron microscopy reveals subepithelial electron-dense deposits on the outer aspect of the GBM, effacement of the foot processes, and expansion of the GBM by deposition of new extracellular matrix between the deposits. These spikes are best seen with Jones' silver stain.

There are several histopathologic characteristics that can distinguish primary MN from secondary MN. Among patients with primary MN, the dominant IgG subclass seen in the subepithelial deposits is IgG4 (noncomplement activator). In secondary MN, IgG1, IgG2 and/or IgG3 (complement activators) are usually the dominant subclass. The deposits in primary MN are exclusively subepithelial or intramembranous. Subendothelial or mesangial deposits can suggest the presence of circulating immune complexes, characteristic of secondary MN. The presence of tubulo-reticular inclusion bodies or a "full house" pattern on immunofluorescence can be clues to the diagnosis of lupus nephopathy (Jennette et al. 1983).

Clinical Manifestations

Classic nephrotic syndrome, including heavy proteinuria, edema, hypoalbuminemia, and hyperlipidemia is the presenting clinical picture in 70–80% of new diagnoses of MN (Noel et al. 1979). The remaining 20–30% have proteinuria, non-nephrotic range. Among nephrotic patients, the onset of edema is typically more gradual than what is seen in minimal change disease or focal segmental glomerulosclerosis. Microscopic

hematuria is common, reported in 69% of children and adolescents with either idiopathic or secondary MN (Chen et al. 2007). Macroscopic hematuria has also been described in children with MN, up to 30% among children of Asian descent (Tsukahara et al. 1993; Wang et al. 2011). Hypertension is seen in about 10%. Renal function, as measured by serum creatinine and/or cystatin C, is typically normal at initial presentation. This contrasts with adults who are diagnosed with MN, in whom renal function is often diminished at the time of diagnosis.

Complications of clinical nephrotic syndrome are well known and include infection, renal insufficiency, and thromboembolism. It is important to note that thromboembolism is more common among patients with MN than among patients with other underlying histopathologic diagnoses. Among children, the risk of thromboembolism in nephrotic syndrome as a whole has been reported to be just under 3%. Among adolescents with MN, that risk has been reported up to 25% (Kerlin et al. 2012). The risk of thromboembolism among secondary forms of membranous nephropathy has not been well described or differentiated from the risk among patients with primary MN.

Secondary Causes of Membranous Nephropathy in Children

Autoimmune Disease

The most common autoimmune disease associated with MN is systemic lupus erythematosus (SLE) (see Chapter XX). Membranous lupus nephritis, also termed class V, can be the initial presentation of SLE. Among patients with new onset SLE, it is not uncommon for serum complement levels to be initially normal and for dsDNA antibodies to be absent. Thus early on, nephrotic syndrome may be the sole feature of the systemic disease. The clinical presentation of class V lupus nephritis is typically associated with preserved renal function.

Several pathological features suggest lupus as the underlying etiology of MN and can offer a clue to the diagnosis before systemic signs or symptoms of the disease. The presence of intraendothelial tubule-reticular structures seen on electron micrograph (EM) is a clue to the diagnosis of SLE, as is mesangial hypercellularity on light microscopy (LM), or the presence of subendothelial and mesangial immune deposits (Jennette et al. 1983; Hogg et al. 1986). Membranous lupus nephropathy can also be associated with full house immunofluorescence staining, including IgG, IgA, and IgM; C3; and C1q.

MN has been described as a rare complication among patients with chronic inflammatory bowel disease. A recent review of the renal complications of inflammatory bowel disease highlighted ESRD caused by several different glomerular diseases. Two of 25 cases had biopsies with the finding of membranous nephropathy. One of the cases occurred in a patient with Crohn's disease, the other was a patient with ulcerative colitis. Several case reports have described children with Crohn's disease and autoimmune enteropathy in association with membranous nephropathy. The mechanism for these associations is not yet well described (Ridder et al. 2005; Colletti et al. 1991).

Eosinophilic gastroenteritis is an uncommon and heterogeneous disease characterized by eosinophilic infiltration of the gastrointestinal tract. The disease can present at all ages, including among children. In as yet unpublished data, our group has identified a patient with secondary membranous nephropathy associated with eosinophilic gastroenteritis. In this patient, while the enteritis improved with the use of corticosteroids, the nephropathy did not, eventually recurring following transplantation.

Infection

Hepatitis B virus-associated Membranous Nephropathy (HBV-MN) has become rare in developed countries, where hepatitis B virus immunization programs are well established in clinical practice. In the USA, children with chronic hepatitis B infection are likely to have immigrated from endemic areas where they may have been infected perinatally. Among children with chronic hepatitis B infection, renal

manifestations are relatively common. The most common manifestation is MN. When present, the hepatitis B surface antigen is typically positive, as is the anti-core antibody and usually the hepatitis B e antigen. Often the patients are asymptomatic carriers with normal or only mildly elevated serum transaminases. By biopsy, the e antigen and anti-e antibody are primarily deposited in the glomeruli. An interesting 2015 study out of China, where Hepatitis B is endemic, demonstrated that 64% of 39 patients with HBV-MN were renal PLA_2R positive and tested positive for the presence of PLA_2R antibodies (Xie et al. 2015). In children with HBV-MN, spontaneous resolution of proteinuria has been described (Lai et al. 1991).

Hepatitis C virus can also be associated with renal manifestations. Among patients infected with hepatitis C, the most common renal manifestation is a membranoproliferative glomerulonephritis histopathological pattern with mixed cryoglobulinemia representing up to 50% of cases. FSGS has been described infrequently. MN can also be present. One study of renal biopsies among patients with the Hepatitis C virus found that 18% of the patients had the MN lesion.

Syphilis has been associated with MN in children. The data is derived from several studies that were completed in the early to mid-1970s (Gamble 1975; Hunte et al. 1993; Losito et al. 1979). Nephrotic syndrome and the glomerular disease can be seen in patients with congenitally acquired syphilis or can present during the secondary stage of sexually acquired syphilis, about 4–10 weeks after the initial presentation of disease. Glomerular deposits are thought to contain antibodies specific for Treponema pallidum antigen and immunofluorescence staining may be positive for treponemal antigens. The glomerular disease associated with syphilis typically resolves completely with appropriate treatment of the infection.

Drugs

Several medications have been associated with the development of MN. Classically, several medications that have been used to treat rheumatologic diseases have been cited, including penicillamine, parenteral gold salts, and bucillamine. The use of these drugs in children has been largely replaced by newer medications. More commonly used medications have also been associated, although rarely with MN, including NSAIDs and lithium.

Penicillamine, parenteral gold salts, and bucillamine have long been associated with the development of MN. One hypothesized mechanism is that the medications are thought to convert large circulating immune complexes to smaller ones, which circulate longer and can deposit in glomerular basement membranes (Manabe et al. 2015). Another hypothesis is that the medications induce the development of autoantibodies. The incidence among patients treated with penicillamine may be as high as 7%, although it is less among patients treated with parenteral gold salts at 1–3% (Hall et al. 1988; Katz et al. 1984). Proteinuria induced by these medications typically resolves within 6 months of discontinuation of therapy.

Tiopronin, a medication that is structurally similar to penicillamine, is used to treat patients with cystinuria, a condition that leads to an increased risk of forming cystine stones. Approximately, 30 cases of nephrotic syndrome have been reported in association with tiopronin, mostly in children. Of those who were biopsied, most demonstrated MN. Resolution occurred in most patients following discontinuation of the medication (Zheng et al. 2014).

NSAIDs are associated with several mechanisms of acute and chronic kidney injury, primarily related to the inhibition of cyclooxygenase enzymes and subsequent reduction in prostaglandin synthesis which can lead to renal ischemia. Classical interstitial nephritis is also commonly described and can be associated with nephrotic range proteinuria, usually secondary to minimal changes by light microscopy. Less commonly, NSAIDs have been associated with MN, typically characterized by rapid remission upon withdrawal of NSAID therapy. Of importance, biopsy in these patients has demonstrated weak IgG4 staining as is common among patients with secondary MN.

Lithium, a medication commonly used to treat manic depressive disorder in children, has been

associated with several forms of nephrotoxicity. The most commonly described are diabetes insipidus, acute tubular necrosis, and chronic tubulointerstitial nephropathy, which combined can impact up to 40% of patients treated with lithium long term. Glomerular injury associated with lithium use is rare. When seen in children, the histopathology can vary, presenting as minimal changes, focal segmental glomerulosclerosis, or MN (Kala et al. 2009; Grunfeld and Rossier 2009; Markowitz et al. 2000). In most cases of glomerular injury, removal of lithium induces remission.

Anti-TNF agents have also been associated with the onset of membranous nephropathy. A case series describing the treatment of several adults with long-standing rheumatoid arthritis with etanercept, infliximab, or adalimumab has reported the temporal association with the development of MN (Stokes MB, Foster K). The mechanism is unclear but may be secondary to immune dysregulation induced by the medications.

Malignancy

Among older adults with membranous nephropathy, up to 20% have been reported to have a malignancy, either a solid tumor or less commonly a hematologic malignancy. Among children, the association is seen, although it is much rarer. Of children with secondary MN, malignancy accounts for about 2%. Excision of the tumor is typically associated with resolution of the nephrotic syndrome (Kohorst et al. 2014).

MN has been reported in association with graft versus host disease. In these patients, IgG4 is typically dominant which is more commonly seen in primary MN rather than secondary forms. In contrast, PLA_2R antibodies is typically negative.

Systemic Illnesses

Several case reports have described MN as a rare association with systemic sarcoidosis in adults. One case report included the association between MN and childhood sarcoidosis, in a 13-year-old adolescent. MN has also been described in a child with common variable immunodeficiency (Yim and Yoo 2012; Dimitriades et al. 1999).

Treatment of Secondary Membranous Nephropathy

The prognosis among patients with secondary MN is usually related to treatment of the underlying disease or infection. In the case of medication-associated disease, removal of the offending medication is usually sufficient to induce remission of the proteinuria. It would be prudent to monitor patients that are currently undergoing treatment with NSAIDs, Tiopronin, lithium, or the anti-TNF alpha class of medications for proteinuria in order to detect renal disease early in its course. Similarly, among patients with malignancy, removal of the tumor is usually associated with remission from the nephrotic syndrome. In contrast, among patients with systemic autoimmune disease or immune dysregulation, the treatment and prognosis is heterogeneous.

Summary

Membranous nephropathy is relatively rare among pediatric patients. When it is seen in children younger than 10 years, a secondary cause is usually identified. As a result, among children with new onset nephrotic syndrome in whom membranous nephropathy is seen on a renal biopsy, a thorough evaluation for a not yet identified underlying disease or infection may be warranted.

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