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EVALUATION OF MEMBRANOUS NEPHROPATHY DIAGNOSTIC AND MANAGEMENT APPROACH

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ABSTRACT

Membranous nephropathy is one of the most common causes of nondiabetic adults' nephrotic syndrome. It accounts for up to 30% of nephrotic syndrome cases in Caucasian adults. It can manifest as a primary or secondary disease, but primary is considered more common. The disease has a waxing and waning clinical course and indolent progress, and immunosuppressive treatment is deemed the mainstay therapy for promoting remission. Although there has been advancement in understanding the pathogenesis of this disease, it still requires further research. We aimed to review the literature to promote the understanding of membranous nephropathy. We reviewed the literature for membranous nephropathy; pathogenesis, etiology, clinical presentation, diagnosis, and treatment. Articles were chosen from the PubMed database, and selected studies were subjected to a thorough review. Membranous nephropathy is one of the most common causes of nephrotic syndrome in nondiabetic adults. The clinical course of this disease is waxing and waning and has indolent progression. Despite the improvement in diagnostic approaches and treatment options, it remains an active field for diagnostic and pharmacological research.

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Introduction

Membranous nephropathy (MN) is one of the most prevalent causes of nondiabetic adults' nephrotic syndrome. It constitutes 20 to 30 percent of nephrotic syndrome cases in Caucasian adults [1]. Membranous nephropathy is based upon the histological changes evident on a light microscope, which includes glomerular basement membrane thickening, with little infiltration or cellular proliferation, and capillary wall thickening [2]. MN occurs most often as a primary and autoimmune-mediated condition; however, it has emerged to be also associated with other conditions and medications [3]. In this review we discuss the pathogenesis, clinical presentation, diagnosis, and treatment.

Materials and Methods

We utilized the PubMed database for the selection process of relevant articles, and the following keys used in the mesh ((“Membranous Nephropathy"[Mesh]) OR (“Pathogenesis"[Mesh] OR "Etiology"[Mesh] OR "Clinical Presentation"[Mesh] OR "Diagnosis"[Mesh] OR "Treatment"[Mesh])). For the inclusion criteria, the articles were selected based on including one of the following: membranous nephropathy or membranous nephropathy’s pathogenesis, etiology, clinical presentation, diagnosis, and treatment. Exclusion criteria were all other articles that did not meet the criteria by not having any of the inclusion criteria results in their topic.

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Results and Discussion

MN accounts for 20-30% of nephrotic syndrome cases in Caucasian adults. White males over the age of 40 are more likely to develop idiopathic MN. While it is less common in females, the presence of MN in young women should raise suspicions about lupus [1, 4, 5]. On the other hand, MN is less prevalent in children, who are more likely to develop it due to hepatitis B or, less commonly, autoimmune or thyroid disease [6].

Pathogenesis

According to MN experimental invented models, MN is immunologically mediated by the deposit of immune complexes on subepithelial space. Immunoglobulin of type IgG acts against the endogenous antigens expressed on or in the proximity of the podocytes processes to form these immune complexes Consequently, they interfere with the barrier function of podocytes and manifest clinically as nephrotic syndrome [7].

The mechanisms behind the pathogenesis of MN have largely been unraveled using the rat model of Heymann nephritis, which closely matches the human disease in clinical and histological aspects. In this model, circulating antibodies attack the endocytic receptor megalin (gp330) expressed on podocyte processes [8, 9]. The immune deposits then activate the complement immune system, causing podocytes' slit diaphragm function to be lost. Consequently, the core manifestation of nephrotic syndrome, proteinuria, ensues [10, 11]. Expression of megalin on podocytes appears to be specific to the rat, and it has been demonstrated that it is not the antigen in human MN. However, other antigens have been demonstrated in human MN [9].

Antigens Linked to Human MN

1- Primary MN

Phospholipase A2 receptor: PLA2R is a transmembrane receptor of M-type expressed on glomerular podocytes. It is expressed in a high quantity on the podocytes and has been recognized as the major antigen in human MN [12]. One study has shown the majority of patients of MN (70%) have circulating autoantibodies directed against this receptor. Moreover, the study demonstrated the correlation of disease activity with the serum concentration of antibodies. Interestingly, this effect of antibodies reaction to PLA2R was evident only in a small percentage of patients with secondary MN [12]. Therefore, PLA2R antibodies have the potential to be of prognostic significance. Some studies have demonstrated that the titers of PLA2R antibodies before the resolution of proteinuria become undetectable [13]. Furthermore, immunosuppressive therapy decreases the levels of PLA2R antibodies. These findings emphasize the importance and utility of PLA2R antibodies in this disease [14].

Thrombospondin type-1 domain-containing 7A: THSD7A is, similar to PLA2R, a transmembrane glycoprotein expressed by podocytes. It was noted to be available in 3-5% of MN patients who were found to have negative titers of PLA2R antibodies. Likewise, it triggers IgG-mediated antibody response [15].

Neutral endopeptidase: Neutral endopeptidase (NEP) was described in 2002 when they found that fetuses born to mothers deficient in NEP developed MN. Antibodies against NEB originated by the mother's immune system crossed the placenta and resulted in MN in the fetus at birth. Renal biopsies revealed an extremely severe type of MN, with the majority of glomerular capillary tufts collapsed. Moreover, the Immunofluorescence study revealed IgG and C3 epithelial deposits. Findings were quite similar to those observed in the adults with MN [16].

2- Secondary MN

In individuals with secondary MN, several antigens have been discovered in the glomerular immune deposits. Infection-related antigens include hepatitis B antigen, treponemal antigen, and Helicobacter pylori antigens. Autoimmune antigens comprise antigens related to systemic lupus erythematosus (SLE); such as Double-stranded DNA, exostosin 1 and 2, and thyroglobulin that is implicated in thyroiditis [17]. Malignancy-related antigens include carcinoembryonic antigen and prostate-specific antigen. Up to this time, the pathogenicity of these antigens has not been established [18].

Etiology

Adult cases of MN account for around 75% of all cases and they are deemed idiopathic [1, 4]. Secondary MN has been linked to several substances or diseases, according to findings that the nephrotic syndrome can be resolved by removing the triggering agent or treating the underlying illness. Notably, it is not applicable to tell the difference between primary and secondary MN only by clinical symptoms. Sometimes, there are certain microscopic and immunofluorescence results that point to secondary etiology [5, 7]. Furthermore, the presence of anti-phospholipase A2 receptor (PLA2R) antibodies in primary but not secondary MN allows for the separation of these two entities in the majority of instances [19].

Causes of Secondary MN

Systemic lupus erythematosus: up to 20% of patients with lupus nephritis develop MN. A group of patients with membranous lupus may present with just kidney disease with no clinical manifestations or serologic findings indicative of lupus. However, such findings may appear after months after the nephrotic syndrome. Lupus should be considered in any young lady who has idiopathic MN [20].

Medications: Drugs that are usually used for treating rheumatoid arthritis have been involved in the occurrence of MN, such as nonsteroidal anti-inflammatory drugs, penicillamine, gold salts, elementary mercury, and anti-tumor necrosis factor agents. The mechanisms behind drug-induced MN are still unraveled [21-25].

Hepatitis B virus infection: MN caused by hepatitis B virus infection typically affects youngsters in endemic regions, with the majority of them being asymptomatic carriers with no active disease state. Liver enzymes are typically normal or moderately raised, and serology reveals positive results for surface antigen, anti-core antibody, and, in most cases, e antigen. It seems that the glomeruli are predominantly deposited with e antigens and anti-e antibodies [6, 20, 26]. Proteinuria resolves spontaneously in children with MN caused by hepatitis B virus infection, but not in adults, many of whom will have a progressive illness [26]. The majority of studies, but not all, found a low frequency of anti-PLA2R antibodies with or without PLA2R staining of immune deposits in MN caused by hepatitis B [12, 14].

Syphilis: MN has been linked to both congenital and secondary syphilis. Immunofluorescence microscopy has recognized Treponemal antigens in the glomeruli, and glomerular deposits have been found to contain antibodies specific for Treponema pallidum antigen. Furthermore, successful syphilis therapy can result in glomerular disease remission [27, 28].

Malignancy: About 5%-20% of MN in the adult population, especially adults beyond the age of 65, have an associated malignancy, most typically a solid tumor such as prostatic cancer, lung, bladder, or gastrointestinal tract. Less common examples include hematologic malignancy such as chronic lymphocytic leukemia [29-32]. The suggested mechanism pertains to tumor antigen accumulation in the glomeruli to increase antibody deposition and complement activation, resulting in epithelial cell and glomerular basement membrane damage and proteinuria [33].

MN with other glomerular disorders: MN may be seen in conjunction with other glomerular diseases. These include diabetic nephropathy, crescentic glomerulonephritis, focal segmental glomerulosclerosis, and IgA nephropathy [34-37].

Clinical Presentation

The majority of MN patients (about 80%) present with nephrotic syndrome; the remaining patients are identified after an examination for silent proteinuria. In contrast to focal segmental glomerulosclerosis (FSGS), significant proteinuria in the absence of hypoalbuminemia is uncommon. As a result of nephrotic syndrome, the patients present with weight gain and lower extremity edema. Proteinuria varies in severity, ranging from sub-nephrotic to more than 20 g/day. Proteinuria is generally evident for numerous months before the MN diagnosis by kidney biopsy is made, highlighting the indolent rate of progression of the disease [38]. Other common urinalysis and urine microscopy abnormalities include oval fat bodies, lipid droplets, and fatty casts. Patients with nephrotic syndrome almost invariably have severe hyperlipidemia at the time of diagnosis, but not those with sub-nephrotic proteinuria [39].

Individuals with MN often have either spontaneous or full or partial remission induced by treatment or chronic nephrotic syndrome with or without gradual development to end-stage renal disease. Long-term prognosis depends in part on the sub-nephrotic proteinuria levels. As long as the levels remain sub-nephrotic (3.5 to 4.0 g/day). These patients, nonetheless, require long-term protein excretion monitoring since many reach the levels of nephrotic proteinuria, which is linked with a greater risk of disease progression [39].

Diagnostic Plan

In the past, it was required to utilize kidney biopsy to diagnose MN; nevertheless, due to the recognition of target antigens and the fair accuracy of anti-phospholipase A2 receptor (PLA2R) serological antibody assays, many physicians prefer to start the diagnostic plan with serology, especially if there are biopsy-related contraindications [40-42].

In individuals with positive anti-PLA2R serology, normal kidney function, and no indication of secondary causes of MN, it is preferable to utilize serologic-based diagnosis tools, which may eliminate the necessity for a kidney biopsy. A negative anti-PLA2R or anti-thrombospondin type-1 domain-containing 7A (THSD7A) serological test may not rule out primary MN, since up to 20% of patients may be seronegative when they present with nephrotic syndrome [40, 41].

In general, a thorough history of all patients with proteinuria that includes the history of drug use such as overuse of NSAIDS, infections like hepatitis B, autoimmune conditions such as SLE, or malignancy is an essential initial step. Afterward, laboratory and radiological assessments can be performed. This includes a full chemistry panel comprising serum albumin, complete blood count, urine analysis, 24-hour urine collection for detecting proteinuria, serology for antibodies and complement levels, tests for viral hepatitis, and chest radiograph or CT for patients with a history of smoking or exposure to asbestosis. Essentially, immunohistology and electron microscopy are used to recognize immune complex deposits in GBM [40, 43].

Management

The treatment of secondary MN relies on treating the underlying etiology [44]. On the other hand, primary MN has several therapy options, including immunosuppressive medications, and drugs for proteinuria such as ACE inhibitors or angiotensin II receptor blockers (ARBs) [45]. Given the high likelihood of spontaneous remission, guidelines advise waiting a period of attentive waiting before contemplating immunosuppressive therapy. If anti-proteinuric treatment with ACE inhibitors or ARBs is started, the chances of spontaneous remission are significantly higher [43]. Immunosuppressive option comprises corticosteroid, cyclophosphamide, tacrolimus, chlorambucil, cyclosporine, mycophenolate mofetil, and rituximab. Cyclophosphamide alternating with a corticosteroid, commonly known as the Ponticelli regime, is frequently recommended as a first-line immunosuppressive treatment for primary MN [46].

The most challenging part of MN is choosing who should be treated with immunosuppressive medication rather than anti-proteinuric medicines. A major part of the issue stems from the inability to anticipate who will proceed to end-stage renal disease, or kidney disease severe enough to necessitate dialysis. Because the medicines listed above are risky, therapy should not be started without careful assessment and weighing the risks and benefits. It is worth noting that corticosteroids alone provide minimal benefit. The focus of treatment in MN is initially first to induce a remission of the nephrotic syndrome, then to avoid the development of end-stage renal failure [47-49].

Conclusion

Membranous nephropathy is one of the most prevalent causes of nondiabetic individuals' nephrotic syndrome. It most often occurs idiopathically, and has a waxing and waning clinical presentation. Studies in the last decades have linked to the presence of anti-phospholipase A2 receptor (PLA2R) antibodies. This discovery has encouraged physicians to follow a serology-based approach to improve the outcomes of the patients. Moreover, immunosuppressive therapy has been shown to promote remissions in patients suffering from this disease. However, it remains an active field for diagnostic and pharmaceutical research

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