WAIS, Marcin, WARCHOŁ, Konrad, JASIURA, Adam, WÓJCIK, Aleksandra & GIŻEWSKA, Kamila. Primary Membranous Nephropathy - what do we know today? Quality in Sport. 2023;13(1):81-87. eISSN 2450-3118. DOI https://dx.doi.org/10.12775/QS.2023.13.01.007
https://apcz.umk.pl/QS/article/view/43714

The journal has had 20 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32582.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32582. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 26.04.2023. Revised: 30.04.2023. Accepted: 09.05.2023. Published: 09.05.2023.

Primary Membranous Nephropathy - what do we know today?

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Abstract
Introduction: Primary membranous nephropathy (PMN) is a common cause of nephrotic syndrome in adults, characterized by the deposition of immune complexes in the glomerular basement membrane.
Aim of this study: evaluate the features of PMN such as incidence, pathology, clinical features and assess the effectiveness of immunosuppressive therapy.
Materials and Methods: The review was based on articles found in PubMed database, using keyword „primary membranous nephropathy" with appropriate sufixes.
Results: PMN is a challenging disease that requires a multidisciplinary approach to diagnosis and management. Laboratory tests, including assessment of autoantibodies and complement levels, are essential for the diagnosis of PMN. Immunosuppressive therapy can be effective in inducing remission in a significant proportion of patients.
Conclusions: Further research is needed to optimize the duration and intensity of immunosuppressive therapy, and to evaluate the role of newer therapies such as rituximab and belimumab.

Keywords: primary membranous nephropathy, nephrotic syndrome, chronic kidney disease

Introduction
Primary membranous nephropathy is the leading cause of nephrotic syndrome in adults and one of the leading causes of end-stage renal disease. It is the most common cause of nephrotic syndrome in adults, accounting for approximately 20-30% of cases [1]. The hallmarks of this condition are edema, hypoalbuminemia, elevated serum lipids, and mainly high levels of protein in the urine. The kidneys of patients with this disease have a significantly thickened glomerular basement membrane, and deposits of immunoglobulins and complement along the walls of the capillaries [2]. The pathogenesis of the syndrome is based on the formation of complexes of immune deposits, including, among others, immunoglobulin G, complement components, and phospholipase A2 type M [3], [4]. PMN is a major cause of chronic kidney disease and end-stage renal disease, and its incidence appears to be increasing worldwide. Despite significant advances in our understanding of the pathogenesis of PMN, its diagnosis, and treatment remain challenging. In this article, we provide a review of the

epidemiology, pathogenesis, clinical features, diagnosis, and treatment of PMN, with a focus on the current challenges and future directions in the field.

Epidemiology and risk factors

The prevalence of MN is approximately 1/100000. The most common manifestation of this disease is PMN, which accounts for 80% of cases, PMN affects twice as many men as women, and in children is rare [5]. In the pediatric population PMN is less severe, more often proteinuria comes with hematuria, and spontaneous remissions are more common than in adults [6].

Based on an analysis of data from 556 cases from three European populations (including French, British, and Dutch), have found the HLA-DQA1 allele on chromosome 6p21 to be strongly associated with PMN in people with white ancestry [7]. Cui et al. [8] in their study among Chinese Han patients identified two independent risk alleles: HLA-DRB1*1501 and -DRB1*0301. In a cohort study, 15 of 154 patients with PMN had circulating autoantibodies anti-THSD7A but not anti-PLA2R1, which may suggest the existence of a distinct group of patients with this disease [9]. Cholesterol, albumin, and proteinuria may be important risk factors for venous thromboembolism in PMN patients, dependent on anti-PLAR2A status, but cholesterol is an important factor for this complication, independent of anti-PLAR2A status [10].

Pathology

PMN is currently believed to be an autoimmune disease, which is mediated by antigen-antibody complexes. These complexes are primarily formed with antigens such as secretory M-type phospholipase A2 receptor (PLA2R), thrombospondin type-1 domain-containing 7A (THSD7A), neutral endopeptidase (NEP), as well as other endogenous antigens. Antigen-antibodies complexes deposit in the lateral basement membrane of the glomerulus, leading to activation of the complement system and further podocytes impairment, which can result in severe clinical symptoms and eventually chronic kidney disease [11].

M-type phospholipase A2 receptor (PLA2R) is a transmembrane glycoprotein belonging to the mannose receptor family, which is expressed on podocytes. Antibodies against PLA2R can be found in kidney biopsy specimens as well as circulating in the blood [12]. The presence of anti-PLA2R-Ab in diagnostic levels has been revealed in 50-80% of patients, as studies show [13]. The presence of anti-PLA2R-Ab and its serum levels corresponds with the disease severity, as in studies anti-PLA2R-Ab serum levels significantly correlated with proteinuria and nephritic-range proteinuria (> 3.5g/day) [14]. High levels of serum anti-PLA2R-Ab also corresponds with a reduced rate of proteinuria remission after the immunosuppressive therapy, as well as an increased risk of reduced renal function measured in eGFR [13]. Furthermore, sustained anti-PLA2R-Ab deposits in the renal biopsy specimens correlated with a disease relapse [15]. Anti-PLA2R antibody are sensitive and extremely specific for diagnosis of PMN, with 80-88% sensitivity and 96-99% specificity, as studies show [13]. Therefore they can be used as a marker for the diagnosis and the activity monitoring of the disease [14].

Thrombospondin type 1 domain–containing 7A (THSD7A) is a podocyte-expressed transmembrane protein. It is expressed in the slit diaphragm domain of foot processes. TSHD7A is believed to be responsible for enhanced adhesion and decreased ability to migrate, therefore it may be responsible for slit diaphragm stability. Hence, anti-TSHD7A-Ab by affecting the slit diaphragm can change its permeability to protein, resulting in proteinuria and further clinical symptoms of PMN [16]. Diagnostic serum anti-TSHD7A-Ab levels have been observed in 2-5% of patients diagnosed with PMN [13]. High serum levels of anti-TSHD7A-Ab corresponded with increased disease activity and decreased response to the treatment [17]. However, anti-TSHD7A-Ab is questioned to be a reliable marker for PMN diagnosis as it specificity is 99%, whereas sensitivity is 4%. THSD7A-AB has a higher diagnostic value in PLA2R-negative patients (sensitivity up to 8%), therefore it can possibly be applied as a diagnostic method for PLA2R-negative PMN patients [18].

Neutral endopeptidase (NEP) was also found to cause PMN in children, whose mothers had miscarriages in their previous pregnancies and were alloimmunized in a passive transplacental mechanism. Children of these NEP-deficient mothers were observed to have circulating anti-NEP antibodies detected after birth, and few of them eventually developed chronic kidney disease, suggesting the cause of their nephron deficiency [19], [20]. Other autoantigens such as superoxide dismutase 2 (SOD2) and aldose reductase (AR) and neural epidermal growth factor-like 1 protein (NELL-1) are studied for potential autoimmunization triggers, especially in PLA2R-negative patients, however, their role in PMN pathogenesis is still uncertain [21], [22].

Clinical presentation

The most common feature of MN is a nephrotic syndrome (NS), with up to 80% of patients presenting nephrotic proteinuria (>3,5 g/d) with other symptoms of NS, such as edema, hypoalbuminemia, dyslipidemia; inducing fatigue, nausea, and abdominal discomfort, being less prominent [23], [24]. If an affected person has

subnephrotic proteinuria and circulating anti-PLA2R antibodies they are more likely to develop nephrotic proteinuria along with worse renal function in later stages [25]. Microhematuria incidence is ranging from 40 to 60%, more often than macrohematuria, which suggests a different type of glomerulonephritis [26], [27]. Hypertension is found mostly in the latter stages of the disease, due to kidney failure [3]. Due to disruption in protein levels, there is an increased risk of thromboembolism, infections and cardiovascular disease, and development of neoplasms [3], [24], [28]. Development of cancer was found to be more common in anti-THSD7A positive patients, and up to 20% of patients in follow-up were reported to develop cancer in 3 years [29], [30].

Diagnostics

For diagnostic purposes, immunofluorescence and electron microscopy can be applied to renal biopsy specimens in order to confirm PMN. In immunohistology granular straining for IgG and PLA2R can be found, deposited subepithelial on the outer surface of the glomerular capillary wall. IgG4 is the predominant class [31]. Complement straining of C3 and C4d with negative C1q are also observed in the deposits, suggesting a non-classical pathway of complement activation. Moreover, in electron microscopy electron-dense deposits can be found in the subepithelial regions of the glomerular basement membrane. Light microscopy is no longer used in PMN diagnostics, as early stages show no pathologic changes. However, in later stages, a homogeneous thickening of capillary walls can be observed on acid-Schiff staining and 'spike and hole' configuration on methenamine silver staining [27].

Apart from microscopic findings in biopsy, blood and urine tests should also be conducted. In urinalysis parameters that should be tested is urine protein; blood level of creatinine and estimated glomerular filtration rate (eGFR); anti-nuclear antibodies (ANA), complement levels, anti-PLA2R and anti-THSD4A immunoglobulins level; HBV, HCV, and HIV to exclude secondary etiology of MN due to viral infection [32], [33].

Assessment of the progression of the disease in each patient, based mainly on proteinuria and kidney function, determines the course of treatment. According to clinical and laboratory criteria, patients are divided into three groups. Patients with normal eGFR, proteinuria <3.5 g/d, and serum albumin >30g/l or a decrease >50% after 6 months of conservative therapy with ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB) are considered to be at low risk. Patients with normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB are in a moderate risk group. Patients with eGFR <60ml/min/1.73m^2 and/or proteinuria >8 g/d for >6 months or patients with normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB and serum albumin <25 g/l are a high risk group. A very-high risk group consists of patients with life-threatening nephrotic syndrome or rapid deterioration of kidney function [3], [34]. Moreover, levels of anti-PLA2R antibodies tightly correlate with the activity of the disease. Low baseline and decreasing levels of anti-PLA2R antibodies predict spontaneous remission, allowing for applying supportive measures alone. High or increasing levels of anti-PLA2R antibodies are a prognosis for nephrotic syndrome and progressive loss of kidney function, thus favoring the initiation of immunosuppressive therapy [33].

Treatment

The first step to treating PMN is introducing patients to general supportive (conservative) therapy [34]. Dietary changes such as restriction of sodium and protein intake [35]–[38], blood pressure control with antihypertensive therapy and renin-angiotensin system inhibitors to minimize proteinuria [39], [40], anticoagulation drugs in select cases [41], hyperlipidemia management with statins [3] and edema control should be applied in order to prevent or modulate the need for immunosuppressive drugs [34].

Patients in a group of low risk should be introduced to general supportive therapy only. Patients with a moderate risk of progression should be either treated with supportive therapy alone or together with rituximab or calcineurin inhibitors with glucocorticoids since many of these patients will develop spontaneous remission [34]. The standard of care for patients with a high risk of progression of PMN is immunosuppressive treatment with cyclophosphamide and steroids combination, rituximab, or calcineurin inhibitors (CNIs) with rituximab [42]. In patients very-high risk of progression, the only recommendation is treatment with cyclophosphamide together with corticosteroids. Such recommendation is based on a study in which alkylating agents improved nephrotic syndrome and the progression of kidney disease over non-immunosuppressive supportive treatment [43].

Cytotoxic therapy with corticoids can be either cyclical or continuous. The cyclical treatment consists of methylprednisolone 1 g i.v. for 3 consecutive days at the start of a month 1, 3, and 5, prednisone 0.5 mg/kg/d in months 1, 3 and 5, together with cyclophosphamide 2.5 mg/kg/d in months 2, 4 and 6. The continuous treatment consists of methylprednisolone 1 g i.v. for 3 consecutive days at the start of a month 1, 3, and 5, prednisone 0.5

mg/kg/d every other day in months 1-6, together with cyclophosphamide 1.5 mg/kg/d in months 1-6. However, daily cyclophosphamide and glucocorticoid regiment is associated with significant toxicity, even among patients treated with lower doses [44].

Tacrolimus is administered in a dose of 0.05-0.1 mg/kg/d, targeting through level 3-8 ng/ml for 12 months. Cyclosporine is administered in a dose of 3.5 mg/kg/d, targeting through level 125-225 ng/ml. Those calcineurin inhibitors are usually given in combination with prednisone in a dose of 10mg/d. If there is no response after 4 months of treatment, it should be withdrawn [34]. As calcineurin inhibitors have various side effects such as potential nephrotoxicity, the duration of therapy should be based on an ongoing assessment of the benefits and risks [45].

Rituximab is a human/murine chimeric monoclonal antibody that targets CD20 molecule on the surface of pre-B cells as well as mature B lymphocytes. It induces the apoptosis of B-cells and reduces the production of autoantibodies including anti-PLA2R antibody [46]. The treatment of PMN with rituximab includes providing the patient with 1.0 g of rituximab twice within 2 weeks together with 375 mg/m^2 of rituximab given 1-4 times at weekly intervals [34]. Rituximab is also used for patients resistant to cytotoxic drugs or CNIs [3].

All patients who are being treated for PMN should be closely monitored for clinical response to therapy. A clinical response is considered in terms of the degree of reduction of proteinuria, where a complete remission is when proteinuria is reduced to <300 mg/d and no clinical remission is when proteinuria is reduced <50% from baseline or is >3.5 g/d [3]. However, in patients with PLA2R-associated PMN, monitoring anti-PLA2R antibody levels may be useful for evaluating treatment response and can be used for further adjustments to the course of treatment [34].

Furthermore, many clinical trials are being conducted to find either new therapeutic agents or new combinations of drugs already registered to treat PMN. Scientists from United States are evaluating the effectiveness of belimumab and intravenous rituximab co-administration at inducing a complete remission of PMN compared to rituximab alone (NCT03949855). What's more, Chinese scientists are recruiting for a study to investigate the safety, tolerability, efficacy and other factors of subcutaneous injection of recombinant humanized anti-CD20 monoclonal antibody in the treatment of PMN (NCT05668403). Finally, daily APL-2 subcutaneous infusion therapy is in the phase II trial to assess its safety and preliminary efficacy in patients with PMN (NCT03453619).

Conclusions

Despite significant advances in our understanding of the pathogenesis and treatment of PMN, there are still many unanswered questions and areas for future research. For example, the optimal duration of immunosuppressive therapy remains unclear, and the long-term risks and benefits of such therapy require further study. Additionally, the role of newer therapies, such as rituximab and belimumab, in the treatment of PMN needs to be further evaluated.

In conclusion, PMN is a complex and challenging disease that requires a multidisciplinary approach to diagnosis and management. With continued research and clinical trials, we hope to improve our understanding of this disease and develop more effective treatments to improve outcomes for patients with PMN.

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