



Lectin Complement Pathway and Diabetes Mellitus in the Pathogenesis of Membranous Nephropathy

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Abstract

Introduction: Membranous nephropathy (MN) is a glomerulonephritis with growing incidence and its pathogenesis still remains unclear, despite discoveries of many new antigens. The understanding of MN pathogenesis has moved from antigen-antibody arena to the complement activation through the lectin pathway.

Aim: Confirm the role of lectin complement pathway in the pathogenesis of the disease and reveal the special role of diabetes mellitus (DM) in idiopathic MN (iMN).

Materials and methods: Materials from 72 renal biopsies with proven MN are used for immunohistochemistry staining (IHC) for phospholipase A2 receptor (PLA2R), immunoglobulin subtype IgG4 and mannose-binding lectin (MBL). Patients are separated in three groups: primary MN (pMN), iMN and secondary MN (sMN). Relationship between the type of MN and IHC deposition is studied. Patients with diabetes mellitus are presented separately. Patients are divided according to IHC results into triple positive/+/+, double positive/+/+, positive /+/+ and triple negative/-/.

Results: Triple /+/+ for PLA2R/ IgG4/ MBL, double /+/+ for PLA2R/IgG4 and /+/+ for PLA2R expression are found only in patients with pMN. Double /+/+ cases for IgG4/MBL are found predominantly in patients with iMN. No cases of double /+/+ for PLA2R/MBL are found. Patients with DM represent 50% of patients with iMN, and 50% of them are double /+/+ for IgG4/MBL.

Conclusions: Activation of the lectin complement pathway is essential in MN. The deposition of MBL is always associated with deposition of IgG4 in pMN and iMN. IgG4 in sMN is not associated with MBL deposition. Possible “switch” from diabetic nephropathy (DN) to MN can be discussed since diabetes is associated with abnormal protein glycosylation and increased activation of lectin pathway.

Keywords

nti-PLA2R, IgG4, MBL, immunohistochemistry

INTRODUCTION

Membranous nephropathy (MN) is one of the most common causes for nephrotic syndrome (in approximately 25% of cases).^[1,2] MN has an increasing prevalence in patients with primary glomerular diseases. In 2016 in China, the leading primary glomerulopathy was IgA nephropathy (28.1%), followed by MN (23.4%). In 2017, MN became the most common primary glomerular disease (43.3%), followed by IgA nephropathy (34.1%).^[3,4] MN has immunocomplex pathogenesis with IgG deposits and complement fractions are deposited on the subepithelial surface of the glomerular basement membrane (GBM) and over time lead to its diffuse thickening. Primary MN (pMN) is a glomerular-specific autoimmune disease that accounts for about 75-80% of MN cases. It has been found that most patients with pMN have circulating antibodies to phospholipase A2 receptor (PLA2R), and other cases of pMN can be classified as idiopathic MN. Secondary MN (sMN) accounts for 20-25% of MN cases, as the cause of which are systemic autoimmune diseases, viral infections, malignancies and drugs.^[5] Anti-M-type phospholipase A2-receptor antibody (APLA2R) has been first described by Beck et al. in 2009, followed by the discovery of another antigen in 2014, namely the thrombospondin type-1 domain-containing 7A (THSD7A), by Tomas and his co-researchers.^[6,7] Recently discovered antigens are EXT1/EXT2, NCAM1, NELL-1 and Sema3B, but the first two are associated with lupus nephropathy, the third one with malignancy and the last one is found in pediatric MN.^[8] The podocyte auto-antigens identified include PLA2R1, THSD7A, and neural epidermal growth factor-like 1 protein (NELL-1), which account for 70–80, 3–5, and 5–10% of pMN, respectively.^[9] Thus, 5-22% of the cases of pMN remain without discovered antigen. We use Laurence Beck, Jr. and David Salant classification^[2] which we adapted in our practice:

- Primary: 75-80%
 - APLA2R associated
 - Another antigen associated (we added this group since there are a lot of new antigens discovered)
 - iMN- The rest of the cases considered primary. It may be associated with different type of immune injury, antibodies to another podocyte/glomerular antigen, or undiagnosed secondary nephropathy.

- Secondary: 20-25%

Haddad et al. demonstrate that anti-PLA2R1 IgG4 auto-antibodies are able to activate the lectin pathway and cause glycosylation-dependent damage to PLA2R1-expressing podocytes, and they also detect cell pathways that mediate this damage. It has also been shown that patients with pMN showed IgG4 glycosylation disorders correlating with disease severity.^[10] Patients with anti-PLA2R1-positive pMN, have increased proportions of galactose-deficient IgG4 glycoforms and galactose deficiency of IgG4 correlated with the titer of antibodies to PLA2R1, as well as the degree of degradation of synaptopodine and NEPH1 in podocytes.

The understanding of MN pathogenesis has moved from antigen-antibody arena to complement one, because even the new discovered antigens did not give us full clarity.

Singh SS et al. found that IgG N-glycosylation patterns in type 2 diabetes is associated with a faster decline of kidney function, reflecting a pro-inflammatory state of IgG. They studied the association between 58 IgG N-glycan profiles and estimated glomerular filtration rate (eGFR). A lack of galactosylation is known to activate the complement system via the lectin pathway by binding to mannose-binding lectin and via the alternative pathway, which induces inflammation. In their study, agalactosylated structures were associated with a faster decline of kidney function, whereas monogalactosylated structures were associated with less kidney function decline.^[11] Their findings are in line with other studies, as agalactosylated IgG glycan structures were also associated with a more rapid eGFR decline in type 1 diabetes and a higher risk of CKD in the non-diabetic population.^[12,13]

AIM

The current study aims to confirm the role of lectin complement pathway in the pathogenesis of the disease and reveal the special role diabetes has in iMN.

MATERIALS AND METHODS

Here we present the data of 72 patients with MN (age range, 24 to 86 years, 41 men and 31 women) treated at the Nephrology Clinic of the Kaspela University Hospital between April 2010 and December 2020. In all patients, the diagnosis was confirmed by kidney biopsy, laboratory tests, including immunological, histopathological, and immunohistochemical tests. We used the following methods:

Kidney biopsy:

All patients had a histologic diagnosis of MN. The kidney biopsy was performed in the Nephrology Clinic of Kaspela University Hospital, Plovdiv.

Indications for biopsy in diabetic patients were:

- Unexplained and rapid increase in proteinuria
- Rapid deterioration of renal function
- Renal impairment in the absence of diabetic retinopathy
- Renal impairment in patients with recent and short-term diabetes mellitus

Immunological studies used are antinuclear antibody (ANA), double-stranded DNA antibodies (anti-dsDNA), anti-cyclic citrullinated peptides (anti-CCP), perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), antineutrophil cytoplasmic autoantibody (cANCA), anti-PLA2R antibodies, thrombospondin (THSD7A), C3 and C4-com-

plement, antiphospholipid and anticardiolipin antibodies and immunoglobulins.

All patients were examined and monitored to follow the course of the disease and the results of treatment.

Pathomorphological examination:

Pathomorphological examinations were performed in the Department of General and Clinical Pathology of Kaspela University Hospital in Plovdiv and in the Department of General and Clinical Pathology of the Military Medical Academy in Sofia.

Immunofluorescence study was performed on 4-micron thick cryostat sections with a standard package of fluorochrome anti-human rabbit antiserum against IgG, IgA, IgM and three complement fractions - C1, C3 and C4, as well as against human fibrinogen. If necessary, capa and lambda light chains were also tested.

Histological and histochemical examination: the puncture kidney biopsies underwent standard paraffin block technique and the following stains were routinely applied to 2 microns thick sections: hematoxylin / eosin, PAS, Masson trichrome, silver impregnation (JMS), amyloid Congo-rot. Amyloid-stained sections were 7-10 microns thick and were observed in polarizing light. Amyloid deposits were determined immunohistochemically.

The immunohistochemical study was performed according to the manufacturer's standard protocols. The used antibodies were from Abcam PLC:

Recombinant anti-PLA2R antibody [EPR20483] (ab211573)

Anti-IgG4 antibody (ab232869)

Anti-mannan binding lectin / MBL antibody [3B6] (ab23457)

Serial sections with a thickness of 4 μ m were made from the paraffin blocks, which were mounted on adhesive glasses. The sections were deparaffinated and rehydrated in alcohols. The washing was performed with Bond™ Wash Solution according to the instructions for use. Prior to the immunohistochemical reaction, heat-mediated antigen recovery was performed by incubation in Bond™ Epitope Retrieval Solution 1 and 2 with pH 9.0 buffer.

The immunohistochemical reaction was performed according to the manufacturer's instructions using Bond Polymer Refine Detection Kit.

Positive and negative controls were prepared for each series of antibody studies.

Interpretation of anti-PLA2R antibody staining results:

Two false-positive models were revealed. The first was characterized by the presence of weak linear expression, localized on the outer surface of the glomerular loop. In the second model, Anti-PLA2R showed more intense, „spotting“ staining in the Bowman space. In contrast to the above described expression, the subepithelial granular dot-

like model was accepted as the only truly positive result. The degree of staining was also assessed - (1+) low expression, (2+) moderate expression and (3+) strong expression.

The lack of IgG4 immunohistochemical expression in the normal kidney represented a complete lack of staining in negative cases and a „dot-like“ pattern in positive cases, making it easier to interpret.

Anti-MBL expression was reported by a similar method - complete lack of staining in negative cases and „dot-like“ pattern in positive cases.

In cases of advanced disease or extensive segmental sclerosis, the immunohistochemical positivity was estimated only in areas of glomeruli without fibrosis, avoiding false negative results.

Statistical analysis:

Most of the data are measured on a dichotomous (There is/Yes – There is not/ No), nominal or ordinal scale. These values are presented in number and percentages, and the following methods are used to establish statistically significant trends: Fisher's exact test for dichotomous quantities and Chi-square test in the presence of more than two categories. The results are illustrated with bar charts.

All statistical analyses were performed at an allowable error level of $\alpha = 5\%$ ($p < 0.05$). The results are graded according to the statistical significance as follows: * - $p < 0.05$; ** - $p < 0.01$; *** - $p < 0.001$. The statistical programs IBM SPSS, version 27 (2020), Minitab version 19 (2020) and MedCalc, version 20.008 (2021) are used for data analysis.

RESULTS

Patients are separated in three groups in accordance with immunological and pathomorphological findings: primary MN (pMN), idiopathic MN (iMN) and secondary MN (sMN).

Data of the frequency and type of deposition are summarized in **Table 1**. Cross-tables and the Chi-square test were used for statistical comparison between MN types and the frequency and type of deposits.

Double-positive patients account for 47% of the pMN group, 33% of the iMN group, and are not detected in the sMN group (0%). The difference between the first two groups (pMN and iMN) and patients with sMN is statistically significant, $p < 0.001$, patients with sMN are positive only for IgG4.

Double-positive patients for APLA2R and IgG4 account for 43% of the pMN group and are not detected in the other two groups (0%), with a significant difference of $p < 0.001$.

Eight patients show double-positive results for IgG4 and MBL, six of which are in the iMN group (33%) and 2 in the pMN group (4%), with a significant difference of 29% ($p = 0.005$). The iMN group also show a significant difference from sMN, in which no double-positive patients are found

Table 1. Frequency of IgG4, APLA2R, and MBL deposits according to the type of MN

Value	pMN (n=45)	iMN (n=18)	sMN (n = 9)	p
Triple positive	12	0	0	
• APLA2R, IgG4 and MBL	(27%)	(0%)	(0%)	0.013*
Double positive	21 (47%)	6 (33%)	0 (0%)	0.000***
• APLA2R and IgG4	19 (43%)	0 (0%)	0 (0%)	0.000***
• APLA2R and MBL	0 (0%)	0 (0%)	0 (0%)	NA
• IgG4 and MBL	2 (4%)	6 † (33%)	0 (0%)	0.005** 0.003**
Positive for one value	12 (26%)	6 (33%)	4 (44%)	0.425
• APLA2R	11 (24%)	0 (0%)	0 (0%)	0.000***
• IgG4	1 (2%)	6 (33%)	4 (44%)	0.000***
• MBL	0 (0%)	0 (0%)	0 (0%)	NA
Triple negative	0 (0%)	6 (33%)	5 (56%)	0.000***

*Statistical significance at $p < 0.05$; **Statistical significance at $p < 0.01$; ***Statistical significance at $p < 0.001$; †Significantly higher relative share compared to pMN group ($p = 0.005$); significantly higher relative share compared to sMN group ($p = 0.003$).

($p = 0.003$).

Double-positive patients for APLA2R and MBL are not detected.

Positive patients for one indicator account for 26% of the pMN group, 33% of the iMN and 44% of the sMN group, but the difference between the MN types do not reach statistical significance, $p = 0.425$. In the pMN group, 24% positive cases for APLA2R are found and not observed in the other two groups (0%), with a significant difference of $p < 0.001$. IgG4-positive patients account for 2% of the pMN group, 33% of the iMN group, and 44% of the sMN patients, with a significant difference between the pMN group and the other two groups, $p < 0.001$. No MBL-positive-only patients are found in any of the groups.

Triple-negative patients predominate among patients with sMN, accounting for 56% of the group. In the iMN group, the triple-negative patients accounted for 33% and 0% in the pMN group, with a significant difference, $p < 0.001$.

Type of IgG4, APLA2R and MBL deposits in patients with diabetes mellitus:

Seventy-nine patients were included in this study allocated into three groups: the pMN group (47 patients), the iMN group (20 patients), and the sMN group (12 patients). For IHC staining there was sufficient material in 72 patients.

Patients with diabetes are 24, sufficient material for IHH had 21 patients. Then we separate these 24 diabetic patients (23 type 2 and 1 patient with type 1) in groups pMN, iMN (type 1 patient included) and sMN on the basis of clinical evaluation and result for APLA2R in serum, we have the following numbers: 11 with pMN, which constitutes 23.4%; 10 with iMN which is 50% and 3 with sMN, which is 25%. The relative share of patients with diabetes is significantly higher in the iMN group compared to the pMN and sMN groups, $p = 0.045$ (Fig. 1).

The frequency of APLA2R, IgG4 and MBL deposits in the pMN, iMN, and sMN groups did not show significant differences between the patients with and without diabetes mellitus ($p > 0.05$ for all comparisons). No significant differences were observed in the total deposits, irrespective of the type of MN, except for a significantly higher percentage of deposits of IgG4 and MBL (23.80%) in the group with diabetes compared to 5.8% in the group without diabetes ($p = 0.042$). (Table 2) Due to this fact the percentage of positive patients to MBL is higher in patients with diabetes. (Fig. 2)

DISCUSSION

Triple positive patients for APLA2R/ IgG4/ MBL, double positive for APLA2R and IgG4 and positivity only for APLA2R are found only in pMN, making the APLA2R a

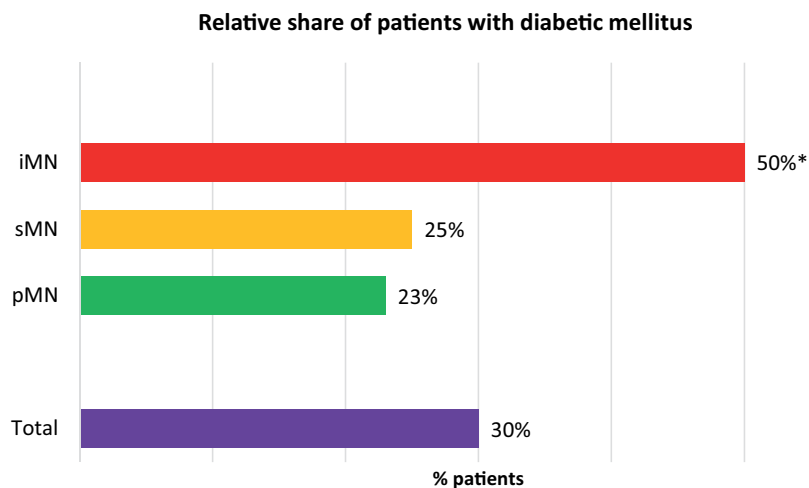


Figure 1. Relative proportion of patients with diabetes in total and by type of MN.

*Statistically significant difference at $p < 0.05$

Table 2. Frequency and percentage of patients with APLA2R, IgG4, and MBL deposits according to the presence or absence of diabetes mellitus and the type of membranous nephropathy

Variables	pMN	iMN	sMN	Total
● with DM	n = 10	n = 8	n = 3	n = 21
● without DM	n = 35	n = 10	n = 6	n = 51
Triple positive				
APLA2R, IgG4, and MBL				
● with DM	2 (20.0%)	0 (0.0%)	0 (0.0%)	2 (9.0%)
● without DM	10 (28.5%)	0 (0.0%)	0 (0.0%)	10 (19.6%)
Double positive				
APLA2R and IgG4				
● with DM	4 (40.0%)	0 (0.0%)	0 (0.0%)	4 (19.0%)
● without DM	15 (42.0%)	0 (0.0%)	0 (0.0%)	15 (29.4%)
APLA2R and MBL				
● with DM	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
● without DM	0 (0.0%)	0 (0.0%)	0 (0.0%)	
IgG4 and MBL				
● with DM	1 (10.0%)	4 (50.0%)	0 (0.0%)	5 (23.8%)*
● without DM	1 (2.8%)	2 (20.0%)	0 (0.0%)	3 (5.8%)
Positive on one parameter				
APLA2R				
● with DM	3 (30%)	0 (0.0%)	0 (0.0%)	3 (14.2%)
● without DM	8 (22.8%)	0 (0.0%)	0 (0.0%)	8 (15.6%)
IgG4				
● with DM	0 (0.0%)	2 (25.0%)	2 (66.0%)	4 (19.0%)
● without DM	1 (2.0%)	4 (40.0%)	2 (33.0%)	7 (13.70%)
MBL				
● with DM	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
● without DM	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Triple negative				
● with DM	0 (0.0%)	2 (25.0%)	1 (33.0%)	3 (14.2%)
● without DM	0 (0.0%)	4 (40.0%)	4 (50.0%)	8 (15.6%)

DM: diabetes mellitus; pMN: primary membranous nephropathy; iMN: idiopathic membranous nephropathy; sMN: secondary membranous nephropathy; MBL: mannose-binding lectin

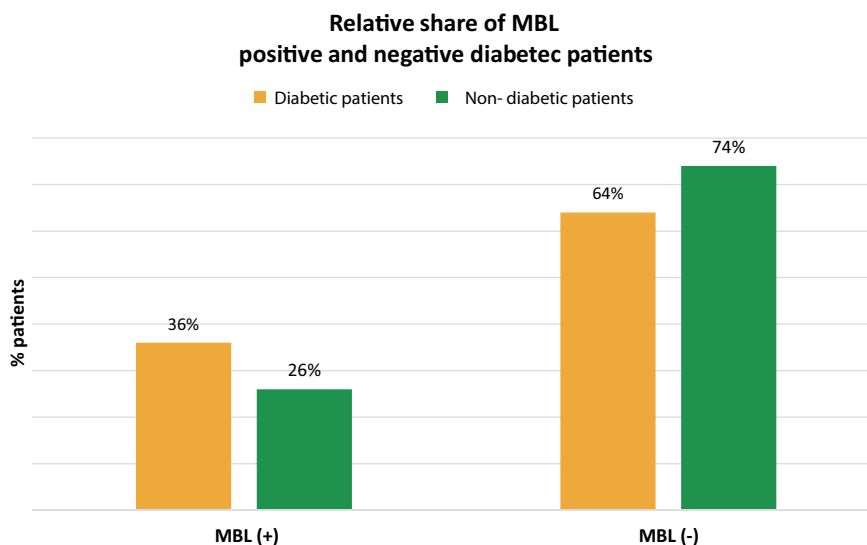


Figure 2. Relative proportion of MBL positive and negative diabetic patients.

truly reliable marker for pMN.

No patients are double positive for APLA2R and MBL, thus showing that IgG4 is needed for the activation of the complement pathway.

The presence of MBL only in patients with pMN and iMN indicates that the lectin pathway is activated in these cases. In the studied literature activation of the complement pathway was referred to cases with pMN, our study shows that the activation of complement pathway has role in iMN also and mainly in patients with diabetes, which represent 50% of patients with iMN, and 30 % of the total group.

The presence of MBL only in combination with IgG4 (with or without APLA2R) proves that IgG4 is required for activation of the lectin pathway.

The presence of IgG4 alone cannot be used as a single marker for pMN or iMN. Single IgG4 deposits predominate in patients with iMN and sMN, mostly in sMN. Patients with sMN have no MBL deposits, they are either negative for any deposits or positive only for IgG4, and complement activation is most likely not via lectin pathway.

No significant differences were observed in the total deposits in patients with diabetes, except for a significantly higher percentage of deposits of IgG4 and MBL, characteristic for iMN.

In the first stage of DN there is a thickening of the GBM, glycation of structural proteins which reduces the anionic filling allowing transition and deposition of immunoglobulins in/on the surface of GBM. During the thickening stage of GBM, collagen binds and accumulates albumin, immunoglobulins and other proteins^[14], but these immunoglobulins trapped there do not lose their ability to form immune complexes with other antigens and antibodies, which can activate the complement cascade. Abnormal protein glycosylation and increased activation of lectin pathway in DM on the background of chronic inflammatory process can

trigger a “switch” from DN to MN. DN stops at the level of thickening of GBM, glycosylation-dependent damage of GBM appears and starts transformation of the pathologic changes to MN. Abnormal glycosylation of immunoglobulins is the initiating factor for complement activation. IgG4 is the most longlasting and subjected to longterm glycation, but it is not the only one. Therefore, to date, we do not have a strict relation between the subtype of deposited IgG and the type of MN. Abnormally glycosylated proteins can be directed against their own altered or unaltered proteins of GBM, or from implanted ones in diabetes and/or chronic inflammatory process. We may never be able to detect all types of antigen-associated MN. iMN will not disappear, even with identification of new antigens. This is closely related to environmental pollution, various daily activities and different chronic inflammatory diseases- infectious, autoimmune or malignant. It is also an important fact that this is more likely to lead to MN in patients with diabetes, who account for 50% of the iMN patients.

CONCLUSIONS

The lectin pathway plays an important role in the pathogenesis of pMN and iMN. Deposition of MBL is always associated with co-deposition of IgG4 in pMN and iMN. There are cases without MBL deposition and these are possibly due to more advanced stage of the disease, when the immunologic inflammation is not so active. The activation of complement in sMN is probably not via lectin pathway. Patients with DM present half of the cases with iMN. We presume that increased activation of lectin pathway in DM on the background of chronic inflammatory process can trigger the “switch” from DN to MN.

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Competing Interests

The authors have declared that no competing interests exist.

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Лектиновый комплементарный путь и сахарный диабет в патогенезе мембранозной нефропатии

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Резюме

Введение: Мембранозная нефропатия (МН) представляет собой гломерулонефрит, заболеваемость которым растёт. Патогенез этого состояния остается неясным, несмотря на открытие стольких новых антигенов. Он переместился с арены антиген-антитело на активацию комплемента через лектиновый путь.

Цель: Целью настоящего исследования явилось подтверждение роли лектинового пути комплемента в патогенезе заболевания и выявление особой роли сахарного диабета (СД) в развитии идиопатических МН (иМН).

Материалы и методы: Материалы из 72 биоптатов почек с подтверждённой МН были использованы для иммуногистохимического окрашивания (ИНС) на рецептор фосфолипазы А2 (PLA2R), иммуноглобулин подтипа IgG4 и маннозо-связывающий лектин (MBL). Пациенты, включенные в это исследование, были разделены на три группы: первичная группа МН (пМН), группа иМН и вторичная группа МН (вМН). Изучена связь между типом МН и отложением ИНС. Отдельно представлены пациенты с сахарным диабетом. По результатам ИНС больные были разделены на тройные положительные, двойные положительные, положительные и тройные отрицательные.

Результаты: Тройной положительный результат на PLA2R/IgG4/MBL, двойной положительный результат на PLA2R/IgG4 и только положительный результат на экспрессию PLA2R были установлены только у пациентов с первичным МН. Двойные положительные случаи на IgG4/MBL встречались преимущественно у больных с идиопатическим МН. Случаев двойного положительного результата на PLA2R/MBL установлено не было. Больные с СД составляли 50% больных с идиопатическим МН, причем 50% из них были дважды положительными на IgG4/MBL.

Заключение: Активация лектинового пути комплемента имеет важное значение при МН. Отложение MBL всегда связано с отложением IgG4 в пМН и иМН. IgG4 в вМН не связан с отложением MBL. Можно обсудить возможный «переход» с диабетической нефропатии (ДН) на МН, поскольку диабет связан с аномальным гликозилированием белков и повышенной активацией лектинового пути.

Ключевые слова

анти-PLA2R, IgG4, иммуногистохимия, MBL