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Original Article

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Presence of M-type Phospholipase A2 Receptor Antibody in Membranous Nephropathy

Özgür Akın Oto[1], Halil Yazıcı[1], Yaşar Çalışkan[1], Ayşe Serra Artan[1], Mehmet Şükrü Sever[1], Egemen Cebeci[2], Savaş Öztürk[2], Aydın Türkmen[1]

[1]Department of Nephrology, İstanbul University School of Medicine, İstanbul, Turkey
[2]Department of Nephrology, Haseki Training and Research Hospital, İstanbul, Turkey

Abstract

Objective: The presence of autoantibodies against M-type phospholipase A2 receptor (anti-PLA2R) is a characteristic of idiopathic membranous nephropathy (IMN). This study aimed to evaluate the presence, levels, and relationship of these antibodies with clinical parameters in idiopathic and secondary membranous nephropathy (MN) and IgA nephropathy (IgAN) in our country by indirect immunofluorescence (IFT) method.
Materials and Methods: A total of 152 adult patients (97 IMN, 11 secondary MN, and 44 IgAN) were included. Serum anti-PLA2R levels were measured by IFT. All the kidney biopsies were evaluated in the same pathology laboratory.
Results: A total of 54 of all patients with IMN were found to be anti-PLA2R-positive, but the patients with secondary MN and IgAN were anti-PLA2R-negative ($p<0.001$). At the time of diagnosis, when no treatment was administered yet, 42 patients were examined for anti-PLA2R, and 32 (76.1%) patients were found to be positive; 64.3% of the patients with currently active disease were anti-PLA2R-positive, and 82.6% of patients with partial or complete remissions were negative ($p<0.001$). In determining the disease activity, the sensitivity of anti-PLA2R was calculated as 73%, specificity as 82%, positive predictive value as 92%, and negative predictive value as 51%. Anti-PLA2R titration was found to be positively correlated with proteinuria. In multivariate analysis of the factors affecting the level of proteinuria, only the presence of anti-PLA2R was significant.
Conclusion: Anti-PLA2R was the main target in most Turkish patients with IMN, and investigation of the presence of anti-PLA2R using IFT is a very sensitive and unique method.
Keywords: Glomerulonephritis, membranous nephropathy, phospholipase A2 receptor

Corresponding Author: Özgür Akın Oto ✉ maviozgurluk@gmail.com
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INTRODUCTION

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. Beck et al. (1) showed the presence of autoantibodies developing against M-type phospholipase A2 Receptor (anti-PLA2R) in 70% of the adult patients with idiopathic MN (IMN), excluding those with secondary MN. Thereafter, it has been shown that anti-PLA2R correlates with disease activity, remission, and relapse (2-4). Hence, it was suggested that monitoring anti-PLA2R level could be helpful in evaluation of disease activity and response to treatment for IMN (5, 6).

It is obvious that studying anti-PLA2R in different races and countries will contribute valuable information to the literature. Therefore, this cross-sectional study, performed for the first time in our country, evaluated the rate of presence of anti-PLA2R in our IMN cohort and relationship of the levels of anti-PLA2R with clinical parameters in IMN, secondary MN, and IgA nephropathy (IgAN).

MATERIALS AND METHODS

In this cross-sectional study, we included 152 adult patients with biopsy-proven IMN, secondary MN, and

idiopathic IgAN. All the kidney biopsies had been evaluated in the pathology laboratory. All patients with IMN and IgAN were negative for antinuclear antibodies, anti-double-stranded DNA, rheumatoid factor, serum hepatitis B virus antigens and antibodies, hepatitis C virus antibodies, tumor markers, and history of toxic agent exposure, and complement C3 and C4 levels were normal. All the data related to the clinical and laboratory parameters were obtained from hospital records. Age, gender, serum creatinine level, albumin level, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglyceride levels, and complete blood count were recorded. Estimated glomerular filtration rates (eGFR) were calculated by the chronic kidney disease epidemiology collaboration equation. Quantification of proteinuria was carried out by measuring the protein:creatinine ratio of a random urine sample as well as 24-hour protein excretion. Decreasing proteinuria (<300 mg/day) with normal serum albumin level and normal renal function were accepted to indicate complete remission. Proteinuria >300 mg/day but <3.5 g/day or a decrease by 50% compared with the highest level with normal serum albumin level and stable renal function were accepted as partial remission (7). Active disease was considered when proteinuria exceeded 3.5 g/day, more than 50% increase in proteinuria, or more than 25% increase in creatinine (7). Serum anti-PLA2R levels were measured by indirect immunofluorescence (IFT) method.

Anti-PLA2R Assay Using IFT Method

First, 10 mL of blood was taken into a tube, and the serum was separated by centrifugation and without using anticoagulant. Preparation of phosphate buffered saline (PBS)-Tween: PBS, 1 package, was dissolved in 1 L of distilled water. Thereafter, 2 mL Tween 20 was added. The solution was mixed slowly after adding Tween-20. The prepared PBS-Tween was used for the dissolution of serums and in the washing stages. Patient samples were prepared in proportions of 1:10, 1:50, 1:100 and 1:1,000 by diluting with PBS-Tween, and 30 µL of the diluted samples were pipetted in order on the reagent tray (IFA incubation tray). They were incubated for 30 minutes at room temperature (18°C-25°C). After incubation, the slides were removed and washed with PBS-Tween. They were kept in the vessel for 5 minutes. The PBS-Tween in the vessel was replaced with new PBS-Tween, and it was likewise washed 2 more times, 5 minutes each. Positive and negative controls and 25 µL fluorescein isothiocyanate-marked antihuman IgG solution were pipetted together with the diluted samples over the reagent tray. After pipetting, the slides that were filled during washing were removed from the vessel, and within 5 seconds, the rear areas of the slides were wiped with paper towels and were immediately covered over the reagent tray. They were incubated for 30 minutes at room temperature (18°C-25°C). After incubation, the slides were removed and washed with PBS-Tween. They were kept in the vessel for 5 minutes and put in the chalet containing PBS-Tween 20 and kept for 5 minutes. Then, the PBS was poured out and new PBS was added. This procedure was performed 3 times. The rear surfaces and corners of the slides removed from the washing vessel were again quickly dried with paper towels and were covered over the prepared lamella. It was checked whether the lamella was fully seated in the inner surface of the slide. The slides were evaluated using a microscope. The patients were grouped according to the presence or absence of anti-PLA2R.

Main Points

- Indirect IFT is a very sensitive method for detection of the presence of anti-PLA2R, which is present in most of Turkish patients with IMN.
- Anti-PLA2R-positive patients have higher creatinine and proteinuria especially in advanced-stage MN.
- Presence of anti-PLA2R is the main independent parameter to determine the level of proteinuria.

The ethics committee approval was receipt for this study from the Clinical Research Ethics Committee of İstanbul University School of Medicine (Approval Date: January 09, 2013; Approval Number: 29). All procedures were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

The statistical analysis was performed with Statistical Package for the Social Sciences for Windows version 16.0 (SPSS Inc.; Chicago, IL, USA). Numerical variables were given as mean±standard deviation. The 2 groups were compared with paired student's t-test or Mann-Whitney U test, when necessary. Chi-squared test with Yates correction and Fisher's exact test were used for 2×2 contingency tables when appropriate for non-numerical data. Correlations between numerical parameters were analyzed with Spearman's rho correlation test. Comparisons among two or more groups were performed with analysis of variance or the Kruskal-Wallis H test appropriately. Tukey's honestly significant difference test was used for post-hoc comparisons. Multivariate analysis of the factors affecting the level of proteinuria was performed by linear regression analysis (enter method). A p value of less than 0.05 was considered statistically significant.

RESULTS

Study Population

A total of 152 patients (89 men, 63 women) with a mean age of 45.0±14.5 (range 18-76) years were included in this cross-sectional study. Of these, 97 (63.9%) patients had IMN, 44 (28.9%) had IgAN, and 11 (7.2%) had secondary MN. The features of the patient groups are given in Table 1. Of the patients with IMN, 20 (20.6%) never received immunosuppressive therapy (IST), 60 (61.9%) received or were receiving IST, and for 17 (17.5%), the de-

cision to treat with IST or not was not made yet. The drugs used solely or in combination by these 60 patients were as follows: steroids, 55 (91.6%) patients; cyclosporine A, 33 (55.0%) patients; tacrolimus, 4 (6.7%) patients; mycophenolate mofetil, 11 (18.3%) patients; azathioprine, 9 (15.0%) patients; cyclophosphamide, 2 (3.3%) patients; and rituximab, 4 (6.7%) patients.

Anti-PLA2R Status

The 54 (55.7%) patients with IMN involved in the study were anti-PLA2R positive, but all the patients with secondary MN and IgAN were negative (p<0.001) (Figure 1). Anti-PLA2R positivity was found at 1/10, 1/50, 1/100, 1/1,000 titer in 7, 14, 18, and 15 patients, respectively. The number of patients examined for anti-PLA2R at the time of diagnosis were 42; it was found that 32 patients (76.1%) were positive, and 10 (23.9%) patients were negative (p<0.001). In 32 patients who were found to be anti-PLA2R-positive at the time of diagnosis, the level of anti-PLA2R was 1/1,000 in 11 of them, 1/100 in 13, 1/50 in 5, and 1/10 in 3.

In the 51 patients included in the follow-up and whose disease activity data were available, 18 (64.3%) of the 28 patients with active disease were anti-PLA2R-positive. In the partial or complete remission group, 19 (82.6%) of 23 patients were anti-PLA2R-negative (p<0.001) (Figure 2). Of the 23 patients with partial remission, 4 (17.4%) were anti-PLA2R-positive, and none of the patients with complete remission were found to be anti-PLA2R-positive. Moreover, 2 patients in whom no response could be achieved with any immunosuppressive treatment, anti-PLA2R level 1/1,000 was found to be positive. In determining the disease activity (in or not in remission), the sensitivity of anti-PLA2R was calculated as 73%, specificity as 82%, positive predictive value as 92%, and negative predictive value as 51%.

It was determined that anti-PLA2R-positive patients had higher creatinine and proteinuria levels at the time of diagnosis and were at a more advanced stage of MN (Table 2). Table 3 shows the data of the patients in whom anti-PLA2R was examined only at the time of diagnosis.

Correlation and Multivariate Analysis

It was observed that anti-PLA2R titration negatively correlated with age (r=-0.34, p<0.001), serum albumin (r=-0.48, p<0,001), total and LDL cholesterol (r=-0.43, p<0.001 and r=-0.26, p=0.005, respectively), and triglyceride (r=-0.23, p=0.027), whereas proteinuria showed a positive correlation (r=0.54, p<0.001). No correlation could be determined with serum creatinine (r=-0.17, p=0.83) or eGFR (r=-0.72, p=0.63).

In a multivariate analysis of the factors affecting the level of proteinuria in patients with IMN, the presence of anti-PLA2R predicted the level of proteinuria, whereas gender, age, serum creatinine, and stage of IMN were not predictive (Table 3).

DISCUSSION

Remarkable improvements were achieved both in disease activity monitoring and treatment response as well as in the dif-

Table 1. Demographic characteristics and laboratory findings of patients with IMN, secondary MN, and IgAN

Characteristics	IMN (n=97)	Secondary MN (n=11)	IgAN (n=44)	p
Age (years)	50.2±14.6	40±15.6	37.1±8.7	0.043*, 0.001**
Follow-up time (months)	53.5±45.1	22.4±9.4	14.5±11.1	0.042*, <0.001**
BUN (mg/dL)	24.2±15.2	25.6±28.984	28.7±22.078	NS
Creatinine (mg/dL)	1.32±1.20	1.58±2.52	1.88±1.74	NS
Uric acid (mg/dL)	5.7±1.6	4.2±1.7	6.5±1.8	0.02*
Total protein (g/dL)	5.7±1	5.9±0.8	6.7±0.8	<0.001**, 0.035***
Albumin (g/dL)	3.2±0.9	2.9±0.9	4±0.6	<0.001**, 0.001***
WBC (/mm^3)	8.9±3	8.6±2.7	9.1±2.6	NS
Hemoglobin (g/dL)	12.4±1.9	11.5±1.7	11.6±1.9	NS
eGFR (mL/min/1.73 m^2)	75±35	100±58	64±39	0.019***
Proteinuria (g/day)	5±4	6.3±5.9	1.9±2.2	<0.001**, 0.002***

*IMN versus secondary MN
**IMN versus IgAN
***Secondary MN versus IgAN
BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; IgAN: IgA nephropathy; IMN: idiopathic membranous nephropathy; MN: membranous nephropathy; NS: not significant; WBC: white blood cell

Table 2. Demographic characteristics and laboratory findings of patients with IMN according to the anti-PLA2R status at the time of diagnosis (n=42)

Characteristics		Anti-PLA2R -negative (n=10)	Anti-PLA2R -positive (n=32)	p
Age (years)		42±16	54±15	0.06
Glucose (mg/dL)		87±35	108±35	0.254
BUN (mg/dL)		21±11	30±20	0.409
Creatinine (mg/dL)		0.89±0.54	1.24±0.84	0.04
eGFR (mL/min/1.73 m^2)		112±53	71±33	0.03
Proteinuria (g/day)		5.1±2.7	8.5±3.1	0.004
Albumin (g/dL)		2.7±1	2.4±0.7	0.616
Total cholesterol (mg/dL)		304±77	295±107	0.52
HDL (mg/dL)		56±23	53±15	0.977
LDL (mg/dL)		209±62	198±79	0.52
Triglyceride (mg/dL)		203±115	232±121	0.538
Uric acid (mg/dL)		5.5±2.1	6.1±1.5	0.209
Sodium (mEq/L)		141±2	140±4	0.245
Potassium (mEq/L)		4.3±0.4	4.3±0.6	0.749
Calcium (mg/dL)		9.1±0.3	9.2±0.6	0.283
Phosphorus (mg/dL)		3.8±0.9	4.1±1.2	0.684
ALT (U/L)		21±6	18±8	0.164
AST (U/L)		20±5	21±12	0.511
Total protein (g/dL)		5.4±0.7	5.0±1	0.267
Leukocyte (/mm^3)		7.6±2	9.0±3.1	0.056
Hemoglobin (g/dL)		12.4±1.9	12.3±2	0.824
Hematocrit (%)		37.5±5.7	39.9±11	0.595
Thrombocytes (/mm^3)		280±38	292±81	0.668
Male, n (%)		6 (60)	28 (87)	0.075
Hypertension, n (%)		4 (40)	22 (69)	0.142
IMN stage n (%)	Stage 1	6 (60)	5 (16)	0.015
	Stage 2	4 (40)	21 (65)	
	Stage 3	0 (0)	6 (19)	

ALT: alanine aminotransferase; Anti-PLA2R: autoantibodies against M-type phospholipase A2 receptor; AST: aspartate aminotransferase; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; IMN: idiopathic membranous nephropathy; LDL: low-density lipoprotein

ferentiation between idiopathic and secondary MN, with the knowledge of MN physiopathology along with demonstration of the presence of PLA2R on the surface of human podocytes. The researchers who first identified the antibody, used Western blotting (WB) method (1). However, subsequently, it was shown that indirect IFT method and enzyme-linked immunosorbent assay (ELISA) can also be used for quantifying this antibody (8-10). WB technique is not being used routinely because it is expensive and complex and requires experienced personnel and equipment. Although, recently, similar results have been obtained with ELISA, practical and easily accessible results could not be obtained yet. Because IFT is easy and reliable, we preferred this method in our study.

In our study, which included patients with idiopathic MN, secondary MN, and IgAN, the number of patients with IMN exam-

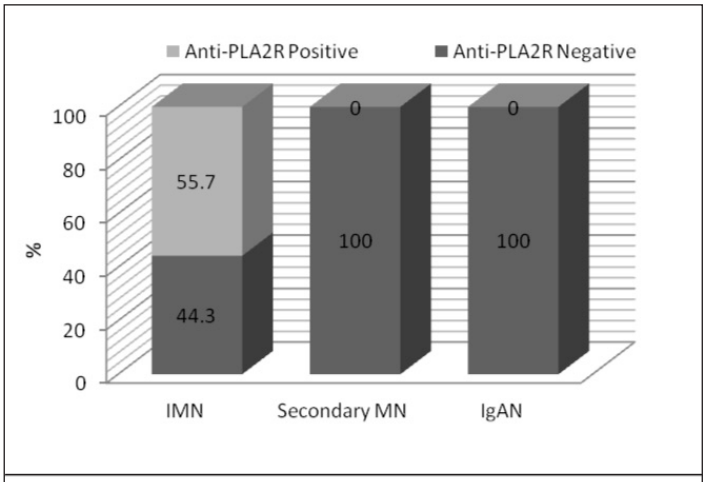

Figure 1. Positivity of autoantibodies against M-type phospholipase A2 receptor in idiopathic membranous nephropathy (IMN), secondary membranous nephropathy, and IgA nephropathy

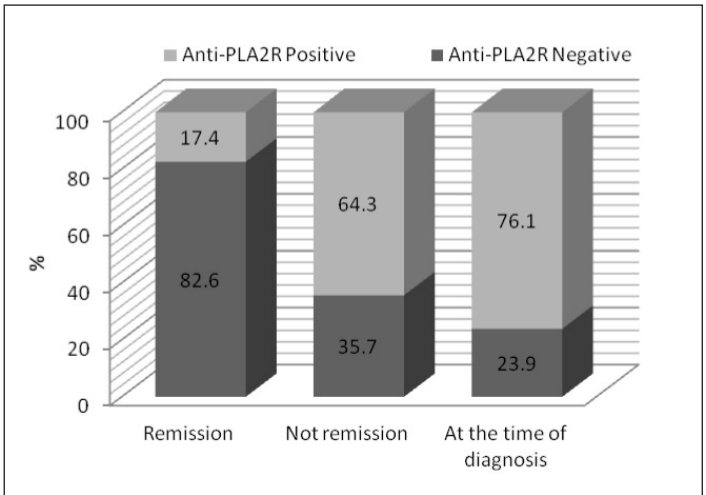

Figure 2. Positivity of autoantibodies against M-type phospholipase A2 receptor in patients with remission, without remission, and at the time of diagnosis in idiopathic membranous nephropathy

Table 3. Linear regression analysis of the factors affecting the level of proteinuria

Factors	B	Beta	p	Lower bound	Upper bound
Constant	0.242		0.468	-0.419	0.903
Gender	-0.081	-0.057	0.571	-0.363	0.202
IMN stage	-0.076	-0.094	0.325	-0.229	0.077
Age (year)	-0.002	-0.046	0.634	-0.012	0.007
Presence of anti-PLA2R	0.835	0.606	<0.001	0.58	1.091
Creatinine (mg/dL)	0.079	0.072	0.469	-0.137	0.295

Anti-PLA2R: autoantibodies against M-type phospholipase A2 receptor; IMN: idiopathic membranous nephropathy

ined for anti-PLA2R during diagnosis was 42; 32 (76.1%) patients were found to be anti-PLA2R-positive, and 10 (23.9%) patients were anti-PLA2R-negative (p<0.001). Beck et al. (1) determined positivity in the samples from 26 of 37 (70%) patients with IMN by using the WB method. In another study by Hofstra et al. (4) performed on the European population with a limited number of patients using the same method, a higher positivity rate (77.8%) was noted. In other studies, anti-PLA2R positivity rates were reported as 57% by Debiec and Ronco (10), 82% by Qin et.al. (11), and 75% by Kanigicherla et al. (9). These values are very similar to the values we obtained (76.1%) when we examined patients with IMN. When all the patients with IMN were included (including those in remission), we determined that 54 (55.7%) of all patients with IMN were anti-PLA2R-positive (Figure 1). Furthermore, it was determined that anti-PLA2R-positive patients had higher creatinine and proteinuria values during the study and advanced-stage MN (Table 2). In multivariate analysis of the factors affecting the level of proteinuria in patients with IMN, the presence of anti-PLA2R predicted the level of proteinuria, whereas gender, age, serum creatinine level, and stage of IMN were not predictive (Table 3). All these data show that assessment of PLA2R is a reliable tool for diagnosis of MN and a prognostic indicator in MN.

In many studies, patients with secondary MN have been found to be anti-PLA2R-negative (1, 8). However, contradictory results have also been reported in the literature (11). Of the 28 patients with active disease in our study, 18 (64.3%) were found to be anti-PLA2R-positive and in partial or complete remission group, and 19 (82.6%) of 23 patients were anti-PLA2R-negative (p<0.001) (Figure 2). None of the patients in complete remission were found to be anti-PLA2R-positive. In determining whether the disease was in remission, the sensitivity of anti-PLA2R was calculated as 73%, specificity as 82%, positive predictive value as 92%, and negative predictive value as 51%. In our study, the number of patients was small; however, this information is consistent with the literature. Although the number of patients was relatively small in our secondary MN and IgAN patient groups, all patients were anti-PLA2R-negative (1, 8).

In our study, anti-PLA2R titration showed a negative correlation with serum albumin level (r=-0.48, p<0.001) and total and LDL cholesterol (r=-0.43, p<0.001 and r=-0.26, p=0.005, respectively), whereas proteinuria showed a positive correlation (r=0.54, p<0.001). Moreover, in the multivariate analysis, we found that the presence of anti-PLA2R was the main independent parameter determining the level of proteinuria (Table 3). In their study using a method similar to ours, Hoxha et al. (8) determined the antibody positivity with dilutions from 1/10 to 1/3,200 in 52% of the 100 patients with primary MN, and a higher antibody positivity rate was determined in patients with nephrotic proteinuria than in those with subnephrotic proteinuria. Hence, there are studies in the literature showing that anti-PLA2R can be used in IMN to exclude secondary causes in diagnosis, in predicting spontaneous remission and relapse, or in evaluating the treatment response (2-4, 9). Furthermore, in many studies, a strong correlation has been shown between anti-PLA2R titers and disease activity (4, 12). Our study also showed data supporting such studies.

Our study had a few limitations. Because it was a cross-sectional analysis, many confounding factors prevented advanced interpretation of the results. The effect of immunosuppressive drug dosage and duration of the treatment on antibody presence and titers could not be tested. We could not test the possible relationship among the possibility of spontaneous remission and long-term disease activation with antibody presence and titers. We could not examine the presence of PLA2R expression in tissue and the relationship of this expression with serum antibody levels and clinical parameters. In contrast, this is the first study investigating the presence of anti-PLA2R in MN, which is the most common primary glomerular disease in our country (13).

CONCLUSION

Indirect IFT is a very sensitive and unique method for detection of the presence of anti-PLA2R, which is present in most Turkish patients with IMN. The anti-PLA2R test can be used in patients with IMN for diagnosis, exclusion of secondary causes, estimation of disease severity, and assessment of the response to the treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of İstanbul University School of Medicine (Approval Date: January 09, 2013; Approval Number: 29).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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