Postprint: Clinicopathological and Short-term Prognostic Analysis of Patients with Idiopathic Membranous Nephropathy with IgG4 and Other IgG Subtype Co-deposition

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Abstract

Objective This study aimed to investigate the clinicopathological features and short-term prognosis of patients with idiopathic membranous nephropathy (IMN) featuring IgG4 deposition combined with other IgG subtypes. Methods Data from 1,099 patients diagnosed with IMN in the Department of Nephrology, First Affiliated Hospital of Zhengzhou University between January 2015 and June 2018 were collected, including 259 cases in the isolated IgG4 deposition group, 259 cases in the IgG4 combined with IgG1 deposition group, 29 cases in the IgG4 combined with IgG2 deposition group, and 57 cases in the IgG4 combined with IgG3 deposition group. The clinical manifestations, renal pathological features, and short-term prognosis were analyzed between the isolated IgG4 deposition group and the IgG4 combined with other IgG subtype deposition groups. Results 1. Compared with the isolated IgG4 deposition group, the IgG1 co-deposition group exhibited higher 24-hour urinary protein quantification clinically and higher positive deposition rates of tissue C3, C4, and λ pathologically (all $P<0.05$). 2. Compared with the isolated IgG4 deposition group, the IgG2 co-deposition group showed a higher C3 deposition rate ($P<0.05$). 3. Compared with the isolated IgG4 deposition group, the IgG3 co-deposition group had higher leukocyte, neutrophil, and monocyte counts, higher 24-hour urinary protein quantification, higher deposition rates of renal tissue C3, C4, and C1q, and more severe renal tubular atrophy and interstitial fibrosis (all $P<0.05$). 4. Compared with the isolated IgG4 deposition group, no significant differences were observed in remission rates at 6 months of treatment among the various groups. Conclusion Patients with IgG4 combined with other IgG subtype deposition exhibited more severe renal clinical and pathological changes than those with isolated IgG4 deposition, though no

significant difference was observed in the 6-month remission rate. This may be related to the varying capacities of different IgG subtypes to fix complement, thereby triggering different intensities of subsequent inflammatory responses.

Full Text

Preamble

Title: Analysis of Clinicopathological Characteristics and Short-Term Prognosis in Idiopathic Membranous Nephropathy Patients with IgG4 Combined with Other Different IgG Subtypes Deposition

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Abstract

Objective: This study aimed to investigate the clinicopathological features and short-term prognosis of idiopathic membranous nephropathy (IMN) patients with IgG4 combined with other IgG subtypes deposition.

Methods: Clinical and pathological data were collected from 1,099 IMN patients diagnosed in the Department of Nephrology at The First Affiliated Hospital of Zhengzhou University between January 2015 and June 2018. Patients were divided into four groups based on IgG subtype deposition patterns: simple IgG4 deposition (n=259), IgG4 combined with IgG1 deposition (n=259), IgG4 combined with IgG2 deposition (n=29), and IgG4 combined with IgG3 deposition (n=57). Clinical manifestations, renal pathological features, and short-term prognosis were compared between the simple IgG4 group and the combined deposition groups.

Results: 1. Compared with the simple IgG4 group, the IgG4+IgG1 group showed significantly higher 24-hour urine protein levels and higher positive deposition rates of C3, C4, and λ in renal tissue (all $P<0.05$). 2. The IgG4+IgG2 group exhibited a higher C3 deposition rate compared to the simple IgG4 group ($P<0.05$). 3. The IgG4+IgG3 group demonstrated higher white blood cell count, neutrophil count, monocyte count, and 24-hour urine protein levels, along with higher deposition rates of C3, C4, and C1q, and more severe tubular atrophy and interstitial fibrosis (all $P<0.05$). 4. No significant differences were observed

in remission rates at 6 months among any of the groups compared to the simple IgG4 group.

Conclusion: IMN patients with IgG4 combined with other IgG subtypes deposition presented more severe clinical and pathological manifestations than those with simple IgG4 deposition, though half-year remission rates showed no significant differences. These findings may be related to varying complement-fixing abilities among different IgG subtypes, leading to differential inflammatory response intensities.

Keywords: Idiopathic membranous nephropathy; IgG subtypes; Complement; Clinical features; Pathology; Prognosis

Introduction

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults, with approximately 80% classified as idiopathic membranous nephropathy (IMN). Notably, 30-40% of IMN patients progress to end-stage renal disease (ESRD) within 5-10 years, underscoring the importance of IMN research [1]. IMN is an autoimmune disease characterized pathologically by IgG and C3 deposition on the outer aspect of the glomerular capillary basement membrane. Approximately 70% of IMN patients express IgG4 antibodies against phospholipase A2 receptor (PLA2R) on podocytes [2], making IgG4 the predominant IgG subtype deposited in pathology. However, IgG1, IgG2, and IgG3 deposition are also frequently observed. Since different IgG subtypes possess varying complement-fixing capacities, they may cause different degrees of renal pathological damage. Currently, no studies have investigated the role of different IgG subtypes in renal pathological injury in IMN. To clarify this role, we analyzed data from IMN patients diagnosed via percutaneous renal biopsy in our department between January 2015 and June 2018, aiming to compare clinicopathological characteristics between patients with simple IgG4 deposition and those with IgG4 combined with other IgG subtypes.

Methods

1.1 Study Population

We collected clinicopathological and treatment data from 1,099 patients with biopsy-proven IMN at The First Affiliated Hospital of Zhengzhou University between January 2015 and June 2018, from which eligible patients were selected. Inclusion criteria: patients with renal biopsy-confirmed IMN. Exclusion criteria: (1) non-MN lesions such as mesangial proliferative glomerulonephritis, focal segmental glomerulosclerosis, or lupus nephritis; (2) secondary MN due to systemic lupus erythematosus, chronic hepatitis B, malignancy, etc.; (3) comorbidities in-

cluding acute renal failure or thromboembolism; (4) IgG4 combined with two or more other IgG subtypes (e.g., simultaneous IgG4+IgG1+IgG2 deposition); (5) fewer than 10 glomeruli in biopsy specimens; (6) incomplete clinical or pathological data; (7) infectious diseases; and (8) follow-up duration less than 6 months.

This study was approved by the Ethics Review Committee of Scientific Research Projects at The First Affiliated Hospital of Zhengzhou University.

1.2.1 Grouping

Based on renal pathological IgG subtype results, selected patients were divided into: simple IgG4 deposition group, IgG4 combined with IgG1 deposition group, IgG4 combined with IgG2 deposition group, and IgG4 combined with IgG3 deposition group.

1.2.2 Clinical Data Collection

Baseline and follow-up data were collected from 604 eligible IMN patients, including age, gender, blood pressure, complete blood count, blood urea nitrogen, serum creatinine, uric acid, serum PLA2R-Ab titer, 24-hour urine protein, pathological diagnosis, treatment regimen, and follow-up measurements of serum creatinine, serum albumin, spot urine protein, and 24-hour urine protein at each visit.

1.2.3 Pathological Assessment

Renal tissue specimens underwent light microscopy, immunofluorescence, and electron microscopy examination. IMN was staged using the Ehrenreich-Churg classification system (Stages I-IV) [3]. For statistical convenience, cases between stages were assigned to the higher stage (e.g., Stage I-II was classified as Stage II). Tubular atrophy, interstitial fibrosis, and arteriolar injury were semi-quantitatively graded according to Guo et al. [4]: tubular atrophy/interstitial fibrosis scored as 0 (0% involvement), 1 (<25%), 2 (25-50%), or 3 (>50%); arteriolar injury scored as 0 (no lesion), 1 (vascular wall thickening), or 2 (vascular wall thickening with luminal narrowing). Immunofluorescence staining intensity <1+ was considered negative, and $ $1+ as positive.

1.2.4 Follow-up and Outcome Definitions

Follow-up began on the date of renal biopsy. Serum creatinine, serum albumin, spot urine protein, and 24-hour urine protein were recorded at each visit within 6 months. Outcomes were defined according to the 2012 KDIGO guidelines: Complete remission (CR) was defined as 24-hour urine protein <0.3 g (or protein-to-creatinine ratio <0.3 g/g) with normal serum albumin and creatinine. Partial remission (PR) was defined as 0.3 g $\leq$ 24-hour urine protein <3.5 g (or protein-to-creatinine ratio 0.3-3.5 mg/g) with >50% reduction from baseline, increased or normalized serum albumin, and stable serum creatinine. All other

cases were defined as non-remission. Remission rate was calculated as (CR + PR) / total cases.

1.3 Statistical Analysis

SPSS 21.0 software was used for statistical analysis. Categorical data from two independent samples were expressed as n (%) and compared using chi-square test, corrected chi-square test, or Fisher' s exact test. Multi-category ordinal data in R×C tables were compared between two groups using Wilcoxon rank-sum test. Normally distributed continuous data from two independent samples were expressed as mean ± standard deviation (sx ±) and compared using t-test or corrected t-test. Non-normally distributed continuous data were expressed as median (25%, 75%) and compared using Wilcoxon rank-sum test. Kaplan-Meier method was used to plot survival curves for poor renal prognosis, with Log-rank test for comparison. P<0.05 was considered statistically significant.

Results

2.1 Comparison of Clinical Characteristics Among Different IgG Subtype Deposition Groups

Compared with the simple IgG4 group, the IgG4+IgG1 group showed significantly higher 24-hour urine protein (P<0.05). The IgG4+IgG2 group showed no significant differences in any parameters (all P>0.05). The IgG4+IgG3 group exhibited higher white blood cell count, neutrophil count, monocyte count, and 24-hour urine protein (all P<0.05). Detailed data are presented in Table 1 .

Table 1 Comparison of demographic and laboratory data between patients with simple IgG4 deposition and IgG4 combined with other different IgG subtypes deposition [n(%), M(25%,75%), sx ±]

Parameter	Simple IgG4 (n=259)	IgG4+IgG1 (n=259)	IgG4+IgG2 (n=29)	IgG4+IgG3 (n=57)
Age (years)	47.00(35.00,58.00)	48.00(38.00,57.00)	49.00(37.00,60.00)	49.00(41.00,59.00)
Gender (male)	142(55.0)	150(57.9)	17(58.6)	37(64.9)
Weight (kg)	68.00(60.80,76.00)	68.00(60.00,76.00)	67.00(62.00,75.80)	70.00(62.90,76.00)
SBP (mmHg)	130.00(120.00,140.00)	131.00(122.00,142.00)	130.00(120.00,142.80)	130.00(123.00,139.50)
DBP (mmHg)	82.00(76.00,90.00)	85.00(78.00,91.00)	80.00(76.30,87.00)	82.00(78.00,89.50)
WBC (10^9/L)	6.50(5.40,8.00)	6.30(5.10,8.40)	6.55(5.08,9.38)	7.29(5.80,9.30)*

Parameter	Simple IgG4 (n=259)	IgG4+IgG1 (n=259)	IgG4+IgG2 (n=29)	IgG4+IgG3 (n=57)
RBC (10^{12}/L)	4.27(3.93,4.65)	4.35(3.94,4.79)	4.36(3.89,4.72)	4.35(4.11,4.88)
Hemoglobin (g/L)	130(119,140)	131(121,145)	129(121.3,139.8)	133(124,144)
Platelets (10^9/L)	228.00(192.00,269.00)	230.00(187.00,264.00)	209.00(174.00,253.00)	225.00(186.00,239.00)
Neutrophils (10^9/L)	3.70(3.00,4.80)	3.60(2.76,5.20)	3.82(2.69,6.21)	4.17(3.40,6.40)*
Lymphocytes (10^9/L)	2.00(1.60,2.46)	2.03(1.50,2.53)	1.78(1.53,2.35)	2.07(1.62,2.70)
Monocytes (10^9/L)	0.46(0.36,0.59)	0.46(0.37,0.60)	0.42(0.33,0.60)	0.50(0.42,0.67)*
Eosinophils (10^9/L)	0.13(0.06,0.22)	0.12(0.07,0.22)	0.14(0.06,0.24)	0.12(0.07,0.18)
Serum K (mmol/L)	4.34(4.10,4.55)	4.26(4.00,4.58)	4.36(4.08,4.50)	4.45(4.06,4.75)
Serum Na (mmol/L)	144.00(141.90,146.00)	143.80(141.00,145.50)	143.50(140.00,146.00)	144.00(142.00,145.75)
Serum Cl (mmol/L)	106.00(103.90,108.20)	106.00(103.00,108.00)	105.00(102.25,109.00)	105.00(103.83,108.00)
Serum Ca (mmol/L)	2.06$\pm$0.14\|2.05$\pm$0.23|0.94(0.88, 1.01)|0.94(0.88, 1.00)|0.			
BUN (mmol/L)	4.72(3.80,5.80)	4.80(3.83,6.00)	4.95(3.98,6.40)	4.7(3.94,6.33)
Serum creatinine (μmol/L)	65.00(55.00,76.00)	65.00(55.00,76.00)	60.50(54,78.75.00)	71.00(58.40,83.00)
Uric acid (μmol/L)	310.00(261.00,376.00)	306.00(260.00,371.00)	299.50(249.00,345.00)	296.00(241.00,371.00)
Serum albumin (g/L)	26.50(21.68,30.05)	25.60(21.55,30.70)	24.60(20.35,27.70)	25.85(23.30,31.20)
24h urine protein (g)	3.37(1.66,6.01)	4.20(2.26,6.94)*	4.31(2.70,6.79)	4.81(2.24,6.79)*

Parameter	Simple IgG4 (n=259)	IgG4+IgG1 (n=259)	IgG4+IgG2 (n=29)	IgG4+IgG3 (n=57)
PLA2R-Ab titer (PU/ml)	29.60(8.90,76.80)	28.80(8.80,92.60)	46.55(11.33,95.90)	29.55(11.20,70.65)

Note: All groups compared with simple IgG4 deposition group; indicates P<0.05*

2.2 Comparison of Pathological Findings and Treatment Regimens Among Different IgG Subtype Deposition Groups

Pathologically, compared with the simple IgG4 group, the IgG4+IgG1 group showed higher positive deposition rates of C3, C4, and λ (all P<0.05). The IgG4+IgG2 group demonstrated a higher C3 deposition rate (P<0.05). The IgG4+IgG3 group exhibited higher positive deposition rates of C3, C4, and C1q (all P<0.05). No statistically significant differences were found in treatment regimens among any groups (all P>0.05). Detailed data are presented in Table 2 .

Table 2 Comparison of pathological findings and treatment regimens between patients with simple IgG4 deposition and IgG4 combined with other different IgG subtypes deposition [n(%)]

Parameter	Simple IgG4 (n=259)	IgG4+IgG1 (n=259)	P	IgG4+IgG2 (n=29)	P	IgG4+IgG3 (n=57)
Immunofluorescence deposition						
IgG	250(96.5)	257(99.2)*		28(96.6)		55(96.5)
IgA	79(30.5)	99(38.2)		13(44.8)		24(42.1)
IgM	6(2.3)	6(2.3)		0(0.0)		1(1.8)
C3	116(44.8)	165(63.7)*		20(69.0)*		36(63.2)*
C4	22(8.5)	44(17.0)*		5(17.2)		15(26.3)*
C1q	4(1.5)	11(4.2)		1(3.4)		9(15.8)*
	8(3.1)	6(2.3)		0(0.0)		0(0.0)
λ	174(67.2)	181(69.9)		22(75.9)		36(63.2)
PLA2R	161(62.2)	187(72.2)*		19(65.5)		33(57.9)
Pathological stage						
Stage I	35(13.5)	47(18.1)		4(13.8)		9(15.8)
Stage II	168(64.9)	169(65.3)		21(72.4)		40(70.2)

Parameter	Simple IgG4 (n=259)	IgG4+IgG1 (n=259)	P	IgG4+IgG2 (n=29)	P	IgG4+IgG3 (n=57)
Stage III	56(21.6)	43(16.6)		4(13.8)		8(14.0)
Tubular atrophy semi-quantitative score						
0	154(59.5)	151(58.3)		19(65.5)		24(42.1)
1	28(10.8)	24(9.3)		2(6.9)		2(6.9)
2	37(14.3)	40(15.4)		6(20.7)		7(12.3)
3	40(15.4)	37(14.3)		2(6.9)		14(24.6)*
Interstitial lesion semi-quantitative score						
0	152(58.7)	147(56.8)		16(55.2)		18(31.6)
1	40(15.4)	40(15.4)		4(13.8)		8(14.0)
2	63(24.3)	67(25.9)		8(27.6)		12(21.1)
3	4(1.5)	5(1.9)		1(3.4)		19(33.3)*
Arteriolar injury semi-quantitative score						
0	126(48.6)	111(42.9)		12(41.4)		21(36.8)
1	64(24.7)	72(27.8)		9(31.0)		17(29.8)
2	69(26.6)	76(29.3)		8(27.6)		19(33.3)
Treatment regimen						
Corticosteroids/Immunosuppressants	202(78.0)	214(82.6)		24(82.8)		48(84.2)
ACEI/ARB	160(61.8)	149(57.5)		15(51.7)		36(36.2)
6-month prognosis						
Complete remission	49(35.8)	42(32.1)		5(35.7)		13(48.1)

Parameter	Simple IgG4 (n=259)	IgG4+IgG1 (n=259)	P	IgG4+IgG2 (n=29)	P	IgG4+IgG3 (n=57)
Partial remission	43(31.4)	58(44.3)		6(42.9)		6(22.2)
Non-remission	45(32.8)	31(23.6)		3(21.4)		8(29.7)

Note: All groups compared with simple IgG4 deposition group; indicates P<0.05*

2.3 Comparison of Prognosis Among Different IgG Subtype Deposition Groups

Within 6 months, the simple IgG4 group achieved complete remission in 49 cases and partial remission in 43 cases; the IgG4+IgG1 group achieved complete remission in 42 cases and partial remission in 58 cases; the IgG4+IgG2 group achieved complete remission in 5 cases and partial remission in 6 cases; and the IgG4+IgG3 group achieved complete remission in 13 cases and partial remission in 6 cases. No statistically significant differences were observed in prognosis among groups (P>0.05), as shown in Figure 1 [Figure 1: see original paper].

Figure 1 Comparison of cumulative remission rates between patients with simple IgG4 deposition and IgG4 combined with other different IgG subtypes deposition

Discussion

Recent studies have shown that the incidence of MN and its proportion among primary glomerular diseases are increasing due to environmental pollution, population aging, and wider application of renal biopsy [5,6]. IMN accounts for approximately 80% of MN cases, making research into its clinicopathological characteristics critically important. IgG4 is the predominant IgG subtype found in IMN immune complexes, while IgG1, IgG2, and IgG3 are more commonly detected in secondary MN associated with malignancy, lupus, infection, or drugs [7-9]. However, in IMN, IgG4 deposition is often accompanied by small amounts of other IgG subclasses [10].

By comparing patients with simple IgG4 deposition versus those with IgG4 combined with other IgG subtypes, we found that combined deposition patients exhibited varying degrees of renal dysfunction and pathological changes, likely related to differential complement-fixing capacities among IgG subtypes and subsequent variations in inflammatory response intensity. IgG is classified into four subclasses (IgG1, IgG2, IgG3, IgG4) based on differences in heavy chain

antigenicity and disulfide bond positions/numbers. While immunoglobulins exert biological effects through multiple effector systems, the most important effector functions for IgG antibodies are mediated through complement and Fc receptors (Fc-Rs). Differences in IgG subclass affinity for Fc-Rs result in varying inflammatory intensities [11].

The IgG4+IgG2 group showed no significant differences from the simple IgG4 group except for higher C3 deposition rates, possibly due to the weak complement-activating ability of IgG2. IgG2 only targets FcγRIIa on neutrophils and may target FcRIIIa on NK cells and macrophages [12], resulting in similar clinical and pathological injury patterns between the IgG4+IgG2 and simple IgG4 groups.

Previous studies have confirmed that IgG1 and IgG3 primarily exert cytotoxic effects through Th1 cytokines (IFN-γ, IL-2, TNF-β), while IgG4 mainly participates in immune responses by activating B lymphocytes via the Th2 system [7]. The IgG4+IgG1 and IgG4+IgG3 groups may simultaneously activate both Th1 and Th2 systems, conferring stronger immunological effects than the simple IgG4 group.

Compared with the simple IgG4 group, the IgG4+IgG1 group showed higher positive deposition rates of C3, C4, and λ, along with greater 24-hour urine protein excretion. IgG1 can bind all Fc-Rs, conferring strong complement-activating capacity [13]. Increased C3 and C4 deposition suggests higher levels of membrane attack complex formation, which damages intrinsic renal cells and exacerbates pathological injury, leading to more severe clinical manifestations such as increased 24-hour urine protein.

The IgG4+IgG3 group showed higher inflammatory markers including white blood cells, neutrophils, and monocytes, suggesting a more active inflammatory state. The key pathogenic step in IMN involves immune complex deposition on podocytes that activates complement, ultimately leading to cytoskeletal reorganization, slit diaphragm loss, and proteinuria. Depending on immune complex characteristics, complement activation may occur via alternative, lectin, or classical pathways [14]. IgG1, IgG2, and IgG3 can activate the classical complement pathway through Fc region binding to C1q [15], with IgG3 showing the highest affinity for C1q and Fc-Rs, conferring the greatest complement-activating effect among the four subclasses [16]. In contrast, IgG4 has a rigid hinge region structure where disulfide bonds easily break, forming "half-molecules" comprising one light chain and one heavy chain that can recombine, preventing classical pathway activation [17,18]. IgG4 deposited alone in renal tissue may activate complement via alternative or mannose-binding lectin pathways [19,20]. C1q, the first component of the classical pathway, indicates classical complement activation [21]. The IgG4+IgG3 group showed higher positive deposition rates of C3, C4, and C1q compared to the simple IgG4 group, suggesting that IgG3 may activate the complement system via the classical pathway, either alone or together with predominant IgG4 deposits [22-24]. This causes more severe renal injury, consistent with our finding of more severe tubular atrophy and

interstitial lesions in the IgG4+IgG3 group, which manifests clinically as higher 24-hour urine protein levels.

However, our study found no significant differences in remission rates at 6 months between combined deposition groups and the simple IgG4 group.

This study has several limitations, including its single-center design, relatively small sample size, and lack of long-term follow-up. Further multi-center studies with larger sample sizes and long-term follow-up are needed to investigate the natural history of IMN patients with different IgG subtype deposition patterns.

In summary, IMN patients with IgG4 combined with other IgG subtypes deposition exhibit more severe clinicopathological manifestations than those with simple IgG4 deposition, with the IgG4+IgG3 group showing the most prominent features. These findings highlight the importance of further investigating renal immune complex deposition characteristics.

All authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.