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Original Article

Clinical manifestations of IgA nephropathy combined with thin glomerular basement membrane nephropathy in children

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Abstract

Background: Immunoglobulin A nephropathy (IgAN) and thin glomerular basement membrane nephropathy (TBMN) are the most common causes of persistent hematuria during childhood. The objective of this study is to determine the difference in clinical features and laboratory findings between pediatric patients with IgA deposited TBMN and IgAN alone.

Methods: Between January 2000 and March 2009, 95 children were diagnosed with IgAN by renal biopsy. Clinical features and laboratory findings of patients with isolated IgAN and with IgAN plus TBMN were compared; the children diagnosed with IgAN were compared to 127 children who had been diagnosed with TBMN alone during the same period.

Results: There were 71 (74.7%) of a total 95 patients that were diagnosed with isolated IgAN (Group1); in 24 (25.3%) of the 95 patients IgAN was combined with TBMN (Group 2). There was marked difference in the gender distribution between Group 2 and isolated TBMN patients. The degree of proteinuria and pathologic severity was higher in Group 1 compared with Group 2. Gross hematuria was present in both groups. There were no distinguishing features in the other laboratory parameters.

Conclusion: Patients with both IgAN and TBMN seem to have similar clinical features to patients with isolated IgAN; however, the latter tend to have better pathologic and laboratory findings, compared to the patients with IgAN alone.

Introduction

Thin glomerular basement membrane nephropathy (TBMN) and IgA nephropathy (IgAN) are the most common causes of primary glomerular disease with persistent hematuria in children [1,2]. Since January 1998 in Korea, all school children undergo a mandatory urine screening test for the early detection of chronic kidney disease. Park et al. [3] reported that more than 72.5% of children showing isolated microscopic hematuria in mass school urine screening test were diagnosed with IgAN or TBMN.

Although these two diseases are similar in their clinical features, patients with IgAN tend to have gross hematuria and proteinuria; it is also known that renal impairment and renal failure can occur during the course of the IgAN [4,5].

Some studies have reported patients with TBMN and IgAN, coincidently. These patients showed heavy proteinuria and progression of renal impairment that have similar characteristics to the patient with a prognosis of IgAN alone [6].

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We conducted this study to compare the differences of clinical manifestations between IgAN with TBMN patients and isolated IgAN or TBMN patients during childhood.

Methods

On a retrospective basis, we performed a cross-sectional study. We reviewed the medical records of 222 patients who had been diagnosed with IgAN or TBMN from January 2000 to March 2009 at Kyungpook National University Hospital. We divided 95 patients diagnosed with having IgAN into two groups: patients with IgAN alone were classified into Group 1 and patients with thinning of glomerular basement membrane on electron microscopy, as well as mesangial IgA deposition, were classified into Group 2. We compared the clinical manifestations between these two groups. In addition, we compared these two groups with isolated TBMN patients, who had been diagnosed at our institution during the same period (Group 3).

The diagnosis of TBMN was based on the criteria proposed by Yoshikawa et al. [7] in 1984. Based on this criterion, biopsy of the kidney reveals thinning of the glomerular basement membrane at <250 nm on electron microscopy with normal findings on light microscopy and on immunofluorescence microscopy. The thickness of the glomerular basement membrane was measured as at least more than five capillary loops and is regarded as diagnostic when $>50\%$ of total visible glomeruli are affected. IgAN was classified based on criteria of the Haas' classification [8].

We compared male to female ratio and average age of each group; in addition, we investigated clinical features, laboratory findings, existence of gross hematuria, degree of proteinuria, and blood pressure at the time of renal biopsy. Because of the cross-sectional design, it was not possible to find results of the spot urine protein to creatinine ratio in every patient, so we used the results of a dipstick test using first morning urine.

Statistical analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) and the difference of frequency was analyzed by Chi-square test and analysis of variance (ANOVA). A P value <0.05 was considered to be statistically significant.

Results

Of the 222 children enrolled, there were 95 IgAN patients, and 127 TBMN patients. Of 95 children with IgAN, 71 children (Group 1, 74.7%) were diagnosed with isolated IgAN and in 24 (Group 2, 25.3%) IgAN was accompanied by TBMN. The mean age of Groups 1 and 2 were 11.0 ± 2.95 (range, 5.3–16.3) years and 10.9 ± 3.04 (range, 6.9–16.4) years, respectively. Male to female ratio was 7:3 in both groups. In Group 3, the mean age was 7.9 ± 2.84 (range 0.5–14.1) years and the male to female ratio was 5:5; the results of Group 2 resembled Group 1 in age and male predominance (Table 1).

Although no patient had gross hematuria in Group 3, all children in Groups 1 and 2 had an accompanying history of gross hematuria.

The average thickness of the glomerular basement membrane in Group 2 was 205.8 ± 31.1 nm. It was thicker than that of Group 3 (183.8 ± 35.7 nm).

There were 33 (46.5%) children with proteinuria of >100 mg/dL in Group 1 and five (20.8%) in Group 2; thus, the patients with isolated IgAN showed more severe proteinuria ($P=0.04$).

Mean systolic blood pressure of Group 1, Group 2, and Group 3 was 115.2 ± 11.40 mmHg, 113 ± 11.79 mmHg, and 109.9 ± 10.0 mmHg, respectively. Mean diastolic blood pressure of Group 1, Group 2, and Group 3 was 63.7 ± 9.26 mmHg, 65.3 ± 5.95 mmHg, and 59.6 ± 7.85 mmHg, respectively ($P<0.01$).

Histologic types of each group by Haas′ classification were as follow: Class I was the most common type (47%), and Class III accounted for 37% in Group 1 (Fig. 1). In addition, in Group 2, Class I was the most common histologic type (63%)

Table 1. Clinical features and laboratory findings of the patients

Findings	IgAN (Group 1)	IgAN+TBMN (Group 2)	TBMN (Group 3)	P^*
Demographic characteristics				
Number	71	24	127	
Sex (M:F)	49:22	18:6	59:68	
Age at biopsy (y)	11.0 ± 2.95	10.9 ± 3.04	7.9 ± 2.84	
Clinical parameters				
Gross hematuria	71 (1 0 0)	24 (1 0 0)	0%	0.92
Proteinuria (<100 mg/dL: >100 mg/dL)	38 (53.5):33 (46.5)	19 (79.2):5 (20.8)		0.04
SBP (mmHg)	115.2 ± 11.40	113 ± 11.79	109.9 ± 10.0	<0.01
DBP (mmHg)	63.7 ± 9.26	65.3 ± 5.95	59.6 ± 7.85	<0.01
Pathologic findings				
Hass Class I–II:III–V	36 (50.7):35 (49.3)	17 (70.8):7 (29.2)		0.08
Thickness of GBM (nm)		205.8 ± 31.1	183.8 ± 35.7	0.04
Laboratory findings				
Hemoglobin (g/dL)	12.7 ± 1.30	12.8 ± 1.10	12.4 ± 0.99	NS
BUN (mg/dL)	11.9 ± 3.54	12.5 ± 6.32	10.3 ± 2.71	NS
Creatinine (mg/dL)	0.7 ± 0.67	0.7 ± 0.32	0.6 ± 0.12	NS
Sodium (mmol/L)	138.6 ± 3.05	138.7 ± 4.93	138.5 ± 2.50	NS
Potassium (g/dL)	4.1 ± 0.35	4.16 ± 0.32	4.2 ± 0.33	NS
Protein (g/dL)	6.8 ± 0.82	7.1 ± 0.35	7.1 ± 0.48	NS
Albumin (g/dL)	4.1 ± 0.56	4.3 ± 0.29	4.4 ± 0.22	NS
Calcium (mg/dL)	9.3 ± 0.66	9.4 ± 0.43	9.4 ± 0.41	NS
Phosphate (mg/dL)	4.6 ± 0.68	4.7 ± 0.73	4.5 ± 0.63	NS

* P is the statistical value between Group 1 and Group 2.
Data are presented as mean $\pm$ SD or n (%).
BUN, blood urea nitrogen; DBP, diastolic blood pressure; F, female; GBM, glomerular basement membrane; IgAN, immunoglobulin A nephropathy; M, male; NS, nonspecific; SBP, systolic blood pressure; TBMN, thin glomerular basement membrane nephropathy.

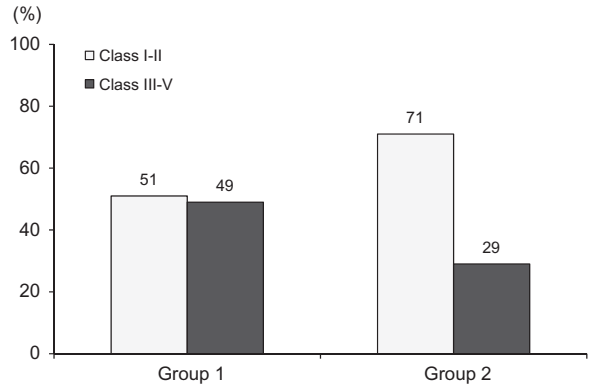

Figure 1. The proportion of Haas′ class of the patients. Group 1, immunoglobulin A nephropathy; Group 2, immunoglobulin A nephropathy with thin glomerular basement membrane nephropathy.

and the next largest group was Class III at 19% (Fig. 1). The ratio of children with Class I–II:Class III–V by Haas′ classification of Group 1 was 35 (49.3%):36 (50.7%) and of Group 2 was 17 (71.9%):7 (29.1%); however, there was no statistically significant difference ($P=0.08$).

There were no significant differences in laboratory findings among these groups (Table 1).

Discussion

Double glomerulopathy that combines two kinds of glomerulonephritis has been reported in several studies and the pathogenesis is still controversial in terms of whether they occur at same time by chance or are a different disease entity to the one disease belonging to another. The frequency of double glomerulopathy was reported to be 6.7% by Bertani et al. [9], 0.5% by Monga et al. [10] and 3.1% by Cheong et al. [11]. In particular, TBMN is known to be commonly accompanied with IgAN [6,12].

Shigematsu et al. [13] reported that focal or diffuse thinning of the glomerular basement membrane is observed in the IgAN patient; since that time, several studies have shown cases of IgAN with TBMN. The first case of TBMN with IgAN was reported by Monga et al. [14] and first pediatric case was reported by Yoshida et al. [15].

The reason for TBMN being frequently accompanied by other glomerulonephiritis is still not known. Lanteri et al. [16] suspected that the thin glomerular basement membrane is more vulnerable to being injured and both TBMN and IgAN are common types of glomerulonephritis, so they may occur accidentally.

In our study, the frequency of the coexistence of TBMN in IgAN patients was 25.3% (24/95), which is less than that found by Chi et al. [17] (37.4%; 19/51). Although several studies were published that the frequency was 1.8% (2/110; Lanteri et al. [16]), 18.5% (10/54; Cosio et al. [12]), they reported frequency of combined IgAN among TBMN patients. Thus, an exact comparison of frequency with our study is not valid, if we analyze the data based on the TBMN patient, the prevalence of the coexistence of the diseases is about 15.8% (24/151) in our study.

We recognized that patients with both IgAN and TBMN are more common in males and all have a history of gross hematuria; thus, the clinical features are very similar to isolated IgAN patient. In addition, Trinn and Nagy [18] reported that patients with both diseases demonstrate a high incidence of gross hematuria.

Research into the prognosis of this condition (IgAN with TBMN) is insufficient, although the majority of investigators suggest that most patients follow the clinical manifestation and prognosis of isolated IgAN. In general, the clinical features of IgAN are comparable with TBMN, but the occurrence of gross hematuria or proteinuria is more predominant in IgAN. In addition, it is known that about 20–30% of patients with IgAN progress to end stage renal disease within 20 years [19]. Norby and Cosio [21] reported that patients with IgAN and TBMN have a worse prognosis compared with isolated TBMN and Berthoux et al. [20] described their prognosis as similar to isolated IgAN. Lanteri et al. [16] revealed that more severe microscopic hematuria and proteinuria, and a higher blood pressure were found in patients with TBMN and IgAN to meet the clinical manifestations of IgAN, although their serum creatinine and creatinine clearance were maintained. Accordingly, the authors suggest that the prognosis for patients with both diseases is related to the degree of mesangial IgA deposition, similar to IgAN.

The ratio of patients with proteinuria >100 mg/dL was 5/24 (20.8%) in IgAN with TBMN group, which is significantly lower than 33/71 (46.5%) in the isolated IgAN group.

Blood pressure was highest in the IgAN group, followed by IgAN with TBMN and TBMN. Although statistical significance was shown, there were no hypertensive patients in Groups 2 or 3, so it is difficult to deduce clinical implication. However, it is evident that patients with IgAN show much higher blood pressure than others.

Although there was no statistical significance, the ratio of patients with higher than Haas Class III on histology was lower in Group 2 (7/24; 29.2%) than in Group 1 (35/71; 49.3%). Unfortunately, most of the studies are based on comparison with isolated TBMN patients; the difference in histological findings and the degree of proteinuria with isolated IgAN patients was unfeasible. However, our results show that proteinuria and histological findings in patients with both IgAN and TBMN are milder than those with isolated IgAN. It is hard to identify the reason for IgAN with TBMN showing less proteinuria than the IgAN. We can speculate that TBMN serves a protective role against IgAN. In order to identify the exact cause, long-term follow-up and additional renal biopsy are needed.

Interestingly, Norby and Cosio [21] reported that when the TBMN accompanied IgAN, the clinical features and prognosis are not worse than for isolated IgAN, although in the case of other glomerulonephritis combined with TBMN showed a more severe outcome. Therefore, it is possible that the thinning of glomerular basement membrane may be associated with a better prognosis for IgAN. Considering that the majority of studies have investigated the characteristics and prognosis based upon TBMN patients, our study is worthwhile from a different point of view as it is based upon that of IgAN patients.

The limitations of our study include the fact that the indication of renal biopsy is diverse so that selection bias can occur. Also the long-term clinical features are not considered. Further research about the long-term clinical course and clinical characteristics are needed for both groups of patients.

Conflicts of interest

None to declare.

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