

Original Article

Clinical characteristics of asymptomatic hematuria children with minor glomerular abnormalities or IgA nephropathy

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Abstract: To investigate and compare clinical manifestations between asymptomatic hematuria pediatric patients with pathological features of minor glomerular abnormalities (MGA) to immunoglobulin A nephropathy (IgAN). From January, 2009 to July, 2011, 96 patients were diagnosed with asymptomatic hematuria at our department. All patients received renal biopsy under B-ultrasound, and then light and electron microscopic investigations of kidney tissues samples as well as immunofluorescence for IgA, IgM and C3 were all performed. Patients with MGA or IgAN were included and analyzed. A total of 86 patients including 57 patients with MGA and 29 patients with IgAN were analyzed in this study. There were significant differences in urinary tract infection ($P = 0.029$), duration of asymptomatic hematuria ($P < 0.001$), hematuria manifestation ($P < 0.001$) as well as proteinuria between the children with MGA and IgAN. Besides, more IgAN (82.8%) patients were complicated with proteinuria compared with MGA cases ($P < 0.001$). Significant differences in IgM ($P = 0.039$) and IgA ($P < 0.001$) were also witnessed between children with MGA and IgAN. Hematuria manifestation, proteinuria and the increased serum IgA could be potential indicators to distinguish asymptomatic hematuria pathologically characterized as MGA and IgAN.

Keywords: Asymptomatic hematuria, pediatric, minor glomerular abnormalities, immunoglobulin A nephropathy

Introduction

Hematuria usually defined as the presence of red blood cells (RBCs) in urine, is considered as a benign manifestation of glomerular injury [1, 2]. These patients barely had other clinical symptoms including hypertension, renal insufficiency or proteinuria [3]. In the pediatric population, although the major etiologies are benign and often asymptomatic, hematuria is also a sign of renal pathology, local infection or systemic disease [4]. Asymptomatic hematuria is macroscopic or usually microscopic, and it may be the only abnormality via neither history nor physical examination providing indication of systemic, renal or urological disorders [5].

Recently, a growing number of children were diagnosed with asymptomatic hematuria. A report showed that in Korea, approximately 396 (26.77%) children were diagnosed with asymptomatic hematuria among 1,478 children who received renal biopsies during 1999

and 2008 [6]. In China, 340 (14.7%) children were diagnosed with isolated hematuria among 2315 children cases of renal biopsies in 1996 [4]. Many factors could lead to asymptomatic hematuria such as nutcracker syndrome, thin basement membrane nephropathy, minor glomerular abnormalities (MGA) and immunoglobulin A nephropathy (IgAN). Among them, MGA and IgAN were the major renal pathologies, and also the focuses of our pediatric nephrologists [7, 8]. It has been proven that renal pathological changes could exert significant effect upon the prognosis of asymptomatic hematuria [9, 10]. Previous study revealed that the cases pathologically characterized as MGA had a favorable prognosis [11] while a study by Szeto et al illustrated that only about 10 (14%) patients with IgAN obtained a favorable prognosis among 72 patients [9]. Moreover, it has been also reported that more than 30% of IgAN cases would progress to end-stage renal failure within 20 years [12]. The difference in prognosis between MGA and IgAN may be caused by the different

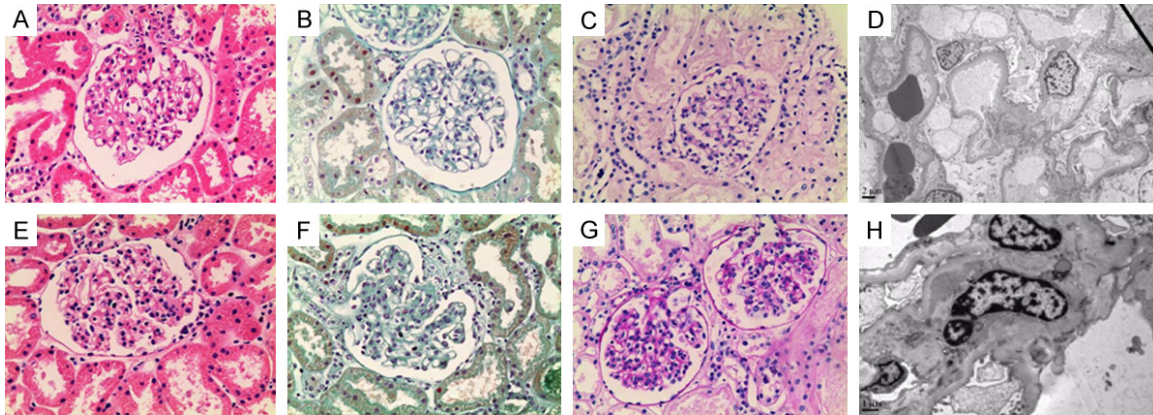


Figure 1. Microscopic examinations of kidney tissues samples in minor glomerular abnormalities (MGA) children (A-D) and immunoglobulin A nephropathy (IgAN) children (E-H) was performed under light microscope (200 ×) after staining with hematoxylin-eosin, masson trichrome, and periodic acid-schiff as well as under electron microscope, respectively.

clinical manifestations. However, few studies have concerned the differences between clinical characteristics of IgAN and MGA.

In this study, we aimed to investigate and compare the clinical manifestations between pediatric patients with asymptomatic hematuria characterized by pathological MGA and IgAN.

Patients and methods

Patients

From January, 2009 to July, 2011, total 96 patients who were diagnosed with asymptomatic hematuria (defined as > 5 red cells in urinary sediment) and received renal biopsy for evaluation of renal diseases were enrolled in this study. The included criteria were: (1) persistent microscopic hematuria or complicated with repetitious macroscopic hematuria; (2) more than 30% of deformed erythrocytes (cri-coid, endospore, and perforation) in urine [13]; (3) no persistent proteinuria (defined as more than 0.5 g/24 h of urinary protein). The patients were excluded when they had (1) edema, hypertension, renal function abnormal or biochemical anomalies in blood; or (2) anomalies in urinary system based on B-ultrasonography. This study had approval from the local ethics committee and was performed in accordance with the Declaration of Helsinki.

All patients received renal biopsy under B-ultrasound. Then light and electron microscopic investigations of kidney tissues samples as well as immunofluorescence for IgA, IgM and

C3 were all performed. Patients with MGA or IgAN were included in this study. Freshly voided urine was collected from patients during their routine visits. Under light microscopy, minor glomerular abnormalities were defined as a slight or no increase in the mesangial matrix (< 4 cells/mesangial area) or cellularity without focal segmental glomerular collapse, scarring, endocapillary proliferation, or adhesions [14, 15]. The definition of IgAN required the presence of dominant or co-dominant glomerular mesangial deposits of IgA as assessed by an immunofluorescence examination [16, 17]. Anybody who had acute post-streptococcal glomerulonephritis, purpura nephritis, lupus nephritis or viral hepatitis type B-related nephritis after clinical and laboratory examinations were excluded.

The demographic data consisting of age, gender, urinary tract infection (which was defined as the presence of greater than 10 organisms/ml and at least 10 leucocytes per high power field in a clean catch specimen) and duration of asymptomatic hematuria were collected. Besides, the clinical and histological examinations for hematuria manifestation, proteinuria (defined as more than a trace on dipstick urinalysis), blood sedimentation as well as IgA, IgM and C3 were also gathered from the records.

Statistical analysis

Data of continuous variables were expressed as mean \pm SD. Data of categorical variable were shown as frequency and percentage.

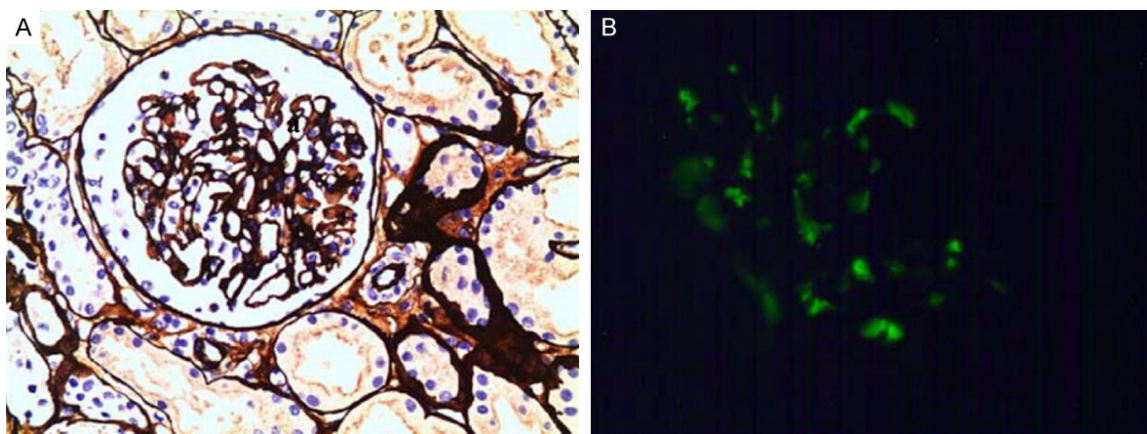


Figure 2. Light microscopic examination (A, 200 ×) of kidney tissues samples after staining with periodic acid-silver methanamine (PASM) and immunofluorescence (B) for IgA in children with immunoglobulin A nephropathy (IgAN).

Table 1. Clinical characteristics of patients in group MGA and group IgAN

Characteristics	Patients with MGA	Patients with IgAN	P-value
Gender, n (%)			0.057
Male	25 (43.8%)	19 (66%)	19 (66%)
Female	32 (56.2%)	10 (34%)	10 (34%)
Male:female	0.78:1	1.9:1	
Age, n (%)			0.346
< 3 years	1 (1.7%)	1 (3.4%)	
3-7 years	13 (22.8%)	3 (10.3%)	
> 7 years	43 (75.5%)	25 (86.3%)	
Urinary tract infection, n (%)			0.029
No	46 (80.7%)	17 (44.8%)	
Yes	11 (19.3%)	12 (41.3%)	
Duration of asymptomatic hematuria, n (%)			< 0.001
< 3 months	9 (15.8%)	21 (72.4%)	
3-12 months	11 (19.3%)	4 (13.8%)	
> 12 months	37 (64.9%)	4 (13.8%)	

MGA, minor glomerular abnormalities; IgAN, immunoglobulin A nephropathy.

Comparisons between MGA and IgAN patients were analyzed by χ^2 test. All statistical analyses were performed using the standard statistical package of SPSS 19.0 (IBM, Armonk, New York). *P*-value less than 0.05 indicated a statistically significant difference.

Results

Among the 96 patients, 10 were excluded due to the mesangial proliferative nephritis or segmented sclerosis at local lesions, without IgA deposition. Thus, a total of 86 children were

analyzed in this study and no one withdrew during investigation. There were 57 patients with MGA and 29 patients with IgAN and no patients showing MGA with IgA deposition were found in the present study. The typical light and electron microscopic investigations of kidney tissues samples were displayed in **Figure 1**. Besides, the immunofluorescence for IgA in IgAN patients was presented in **Figure 2**.

The MGA patients developed asymptomatic hematuria at the age ranging from 3 years to 16.75 years old with duration of asymptomatic hematuria from 4 d to 9 years, whereas the development of hematuria in IgAN patients started at the age between 2.5 years and 14 years old, with duration of disease from 1 week to more than 2 years. There were significant differences in urinary tract infection ($P = 0.029$) and duration of asymptomatic hematuria ($P < 0.001$) between children with MGA and IgAN, whereas no significant difference in gender and age existed between them ($P > 0.05$, **Table 1**). In MGA patients (19.3%), the rate of urinary tract infection was significantly lower than that in IgAN patients (41.3%). As for the duration of asymp-

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Table 2. Comparisons of clinical manifestations between the group MGA and group IgAN

Symptom	Patients with MGA	Patients with IgAN	P-value
Hematuria manifestation, n (%)			< 0.001
Macroscopic hematuria	7 (12.3%)	23 (79.3%)	
Persistent microscopic hematuria	46 (80.7%)	6 (20.7%)	
Intermittent microscopic hematuria	4 (7.00%)	0	
Complicated with proteinuria, n (%)			< 0.001
No	45 (78.9%)	5 (17.2%)	
Yes	12 (21.1%)	24 (82.8%)	

MGA, minor glomerular abnormalities; IgAN, immunoglobulin A nephropathy.

Table 3. Comparisons of erythrocyte sedimentation rate and immunological parameters between group MGA and group IgAN

	Patients with MGA	Patients with IgAN	P-value
Blood sedimentation, n (%)			0.127
Normal	49 (85.9%)	21 (77.7%)	
Increased	8 (14.1%)	8 (22.3%)	
Serum IgA, n (%)			< 0.001
Normal	52 (91.2%)	12 (43.4%)	
Increased	5 (8.8%)	17 (56.6%)	
Serum IgM, n (%)			0.039
Normal	53 (92.9%)	22 (75.9%)	
Increased	0	2 (6.8%)	
Decreased	4 (7.1%)	5 (17.3%)	
Serum C3, n (%)			0.077
Normal	56 (98.2%)	25 (82.7%)	
Increased	1 (1.8%)	4 (17.3%)	

MGA, minor glomerular abnormalities; IgAN, immunoglobulin A nephropathy.

omatic hematuria, most patients (64.9%) have suffered from asymptomatic hematuria for more than 12 months in MGA patients, whereas 72.4% (n = 21) IgAN patients have suffered from asymptomatic hematuria for less than 3 months ago (**Table 1**).

Clinical examinations showed there were significant differences in hematuria manifestation ($P < 0.001$) as well as proteinuria ($P < 0.001$) between MGA and IgAN patients. Persistent microscopic hematuria (n = 46, 81%) was the most common manifestation in MGA patients whereas macroscopic hematuria (n = 23, 79.3%) was the most common manifestation in IgAN patients (**Table 2**). Besides, more IgAN (82.8%) patients were complicated with proteinuria compared with MGA cases ($P < 0.001$).

Table 3 also demonstrated significant differences between MGA and IgAN patients in IgM ($P = 0.039$) and IgA ($P < 0.001$).

Discussion

Asymptomatic hematuria was common in pediatrics in clinical practice. In this study, MGA was the most dominant pathological manifestation in the 96 pediatric patients aged 2-16 years old (57/96, 59.3%), which was in line with a multicenter study in China [18]. Zhai et al reported that there were 45 MGA patients (56.25%) in 80 school-age children (aged 7-14 years old) with asymptomatic haematuria. However, the proportion of IgAN (10%) in the study of Zhai et al was lower than that in this study (29/96, 30.2%). Moreover, Miao et al found that there were 22.6% IgAN patients and 10.7% MGA patients in children (aged 2-17 years old) with asymptomatic hematuria [19]. A previous study have reported that the incidence and number of the IgAN patients aged 7 years old was increased as they grow [20]. Thus, we speculated that the higher proportion of IgAN

patients in this study and the study of Miao et al might be caused by the children aged larger than 14 years old (who were not included in the study of Zhai et al). Meanwhile, different incidence of MGA in children with asymptomatic hematuria may be also caused by the different age distribution among these studies. More studies were required to verify these speculations and explore the factors influencing the incidence of these biopsy-proven renal diseases.

For the clinical characteristics, no significant difference in gender and age existed between children with MGA and IgAN. However, MGA patients had lower rate of urinary tract infection than IgAN patients. The urinary tract infection was one of the common causes of asymp-

omatic hematuria [21, 22]. It has been reported that the elevated urinary secretory IgA was associated with the urinary tract infection in children [23, 24]. Moreover, the occurrence of IgAN is associated with IgA immune response to the infections such as staphylococcus infection, mycoplasma pneumoniae infection and hepatitis C infection [25-28]. Considering these evidences, we speculated that urinary tract infection may stimulate the IgA immune response and then lead to the occurrence of IgAN as these above infection diseases. However, there was still no study reporting the association between infection and MGA. So there were more cases of urinary tract infection in IgAN patients than that in MGA patients. In addition, it was reported that the occurrence of proteinuria was increased progressively with time [29]. Given the difference in duration of asymptomatic hematuria between children with MGA and IgAN in this study, the results on proteinuria may be affected by it. Thus, further studies on comparison between MGA and IgAN patients with similar duration of asymptomatic hematuria were needed to verify the results of this study.

As the two most common pathological manifestations of asymptomatic hematuria, MGA and IgAN also differed in clinical hematuria manifestation. In our study, there were significantly more patients with macroscopic hematuria (79.3%) in children with IgAN than MGA. Similar to this study, the macroscopic hematuria also was the main hematuria manifestation in children with IgAN (52.8%) in the study of Bao et al [30]. The higher proportion of patients with macroscopic hematuria in children with IgAN may be caused by the small sample size in this study. Moreover, this proportion was lower in adults with IgAN (21.3%) [31]. Thus, the macroscopic hematuria may be the main hematuria manifestation in children with IgAN but not adults in China. Further studies with larger sample size were required to confirm the results of this study. In addition, it was reported that IgAN could lead to an increase risk of progression to end-stage renal disease and acute kidney injury suggesting a bad prognosis [2, 32]. Moreover, the macroscopic hematuria in IgAN can lead to the acute worsening of renal function [33]. Meanwhile, negative effect of macroscopic hematuria on long-term of renal function has also been found in IgAN [2]. Thus,

it is important for children with IgAN to timely control macroscopic hematuria during the clinical treatment of IgAN.

For the other clinical hematuria characteristic, there was significant difference in patients with persistent microscopic hematuria between MGA and IgAN patients. Moreover, results showed that the persistent microscopic hematuria was the main hematuria manifestation in children with MGA. Persistent microscopic hematuria was defined by microscopic evidence of 2-5 or more red blood cells per high-power field of urinary sediment [34]. Moreover, previous report had demonstrated that persistent microscopic hematuria was an increased risk for end-stage kidney disease, mainly secondary to primary glomerular diseases [35]. Hence, it was speculated that MGA could also progress into end-stage renal disease to a certain extent. Consequently, it is recommended to make a close follow-up for MGA cases, and evaluate prediction of MGA for end-stage kidney disease.

In addition, it was also displayed that more patients were accompanied with proteinuria in children with IgAN than MGA. Moreover, 21.1% (12/57) patients of MGA showed proteinuria in this study, which was littler higher than that that in the study of Zhai et al (15.1%) [18]. This littler difference may be caused by the different age distribution, sources of participants or duration of asymptomatic hematuria (based on above discussion with the study of Turi et al [29]) between studies. In addition, the incidence of proteinuria (82.8%) in children was similar to that in the study of Zhai et al (80.8%) [18], which indicated that the proteinuria was a main symptom in children with IgAN and may be a potential indicator for IgAN in distinguishing from MGA. As for the serum IgA, more patients had increased serum IgA in children with IgAN than MGA. It was explained that IgAN could lead to the defective IgA glycosylation which could subsequently give rise to the increased levels of IgA [36]. In addition, the difference in IgM between IgAN and MGA should be further confirmed in future studies and the mechanism should be explored.

Furthermore, some limitations of this study should be noted. Firstly, the sample size was small, further studies with larger sample size should be performed. Second, due to the

respective nature of this study, data of tubular basement-membrane disease and hereditary nephritis were not recorded and collected for analysis. Meanwhile, the level of proteinuria also could not be analyzed due to inadequate data in the records. Third, a previous study on Hungary children has concluded that symptoms of isolated hematuria may last for a long-term period [29]. Thus, long term follow up should be performed in the further studies. In addition, generally, a renal biopsy is not needed in patients showing asymptomatic hematuria without proteinuria, because a drug therapy is not needed in them. However, asymptomatic hematuria is associated with some urologic malignancies such as urinary tract neoplasms and bladder cancer [37, 38]. Thus, the renal biopsy was performed in these patients with asymptomatic hematuria without proteinuria for diagnosis of these possible renal diseases with approval from the local ethics committee [39].

In conclusion, macroscopic hematuria, proteinuria and the increased serum IgA could be potential indicator to distinguish asymptomatic hematuria in pediatric patients pathologically characterized as MGA and IgAN, as well as provide a reference for clinical diagnosis.

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Disclosure of conflict of interest

None.

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