Persistent asymptomatic isolated hematuria in children: clinical and histopathological features and prognosis

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Background: **This study involving 351 children who had undergone kidney biopsy secondary to persistent asymptomatic isolated hematuria was undertaken to assess histological diagnosis of the disease and its natural history and prognosis.**

Methods: **The patients were divided into two groups: 215 patients with asymptomatic isolated microhematuria (AIMH; proteinuria <0.1 g/day) and 136 patients with persistent asymptomatic microhematuria, recurrent macrohematuria and/or proteinuria (AMHP; proteinuria 0.1-0.25 g/day). After kidney biopsy, the patients were monitored for 2-10 years.**

Results: **Normal biopsies or minor abnormalities were more frequent in AIMH patients than those in AMHP patients, who exhibited IgA nephropathy more frequently. During the 2- to 10-year follow-up period, adverse renal events (i.e., development of proteinuria, hypertension, or impaired renal function) were observed in 13/215 (6.0%) patients with AIMH and 31/136 (22.8%) patients with AMHP (χ^2=15.521, *P*<0.001).**

Conclusions: **Normal biopsies or minor abnormalities were more frequently observed in AIMH patients, whereas IgA nephropathy and adverse renal events were more frequent in AMHP. Microscopic hematuria, especially when accompanied by macroscopic hematuria and proteinuria, may represent an important risk factor for the development of chronic kidney disease.**

World J Pediatr 2013;9(2):163-168

Key words: **adverse renal events; asymptomatic isolated hematuria; proteinuria**

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doi: 10.1007/s12519-013-0415-3

Original article

Introduction

Hematuria is the first sign of glomerular injury to be noted by ancient physicians and continues to be a frequent manifestation of glomerular disease.[1] Studies[2,3] supporting the current recommendations for evaluation and management of asymptomatic isolated hematuria are long overdue, despite the frequency of this condition in clinical practice. Nephrologists devote more attention to the monitoring and therapeutic targeting of proteinuria, which is another key manifestation of glomerular injury. In contrast to proteinuria, glomerular hematuria has been considered a clinical manifestation of glomerular diseases that does not have real consequences on renal function or long-term prognoses.[4]

However, studies[1,5] have reported that glomerular macroscopic hematuria is associated with the development of acute kidney injury (AKI) with predominant tubular cell damage, and there is increasing evidence to support the negative impact of glomerular hematuria-associated AKI on long-term renal function, both in the context of IgA nephropathy and in anticoagulated patients.

Therefore, we analyzed the clinical features, pathological features and prognosis in 351 children with persistent asymptomatic isolated microscopic hematuria with or without macrohematuria and proteinuria in the present study to evaluate the clinical significance of microhematuria, macrohematuria and proteinuria in the development of glomerular injury and chronic kidney disease.

Methods

Patients

From January 1992 to October 2012, 1810 renal

biopsies were performed at the Department of Nephrology of Children's Hospital, Zhejiang University School of Medicine, which included 351 consecutive individuals (19.4%) diagnosed with persistent asymptomatic isolated hematuria.

Diagnostic criteria

Participants enrolled in the study were initially screened for the presence of microscopic hematuria by the urinary dipstick test, followed by sediment examination by urine microscopy if the dipstick result was positive.

The diagnostic criteria for persistent asymptomatic isolated hematuria included the following: (1) five or more red blood cells per high-power field for urine specimens obtained on three separate occasions on different days (female participants were instructed to avoid testing during menstruation) and recurrent macrohematuria in some patients; (2) no significant proteinuria, with 24-hour urinary excretion of protein less than 0.25 g/day; (3) serum creatinine values within the normal range and without hypertension; (4) no congenital anomalies of the kidney or urinary tract (CAKUT) detected on renal imaging using intravenous pyelographic contrast, B ultrasound or, in some patients, magnetic resonance; (5) being otherwise asymptomatic, with hematuria as the sole finding and not attributable to other known or apparent disease, including systemic lupus erythematosus, urinary tract infections, liver disease, tumors, trauma, drug-induced hematuria, idiopathic hypercalciuria, or urolithiasis.

Idiopathic hypercalciuria was formally defined as 24-hour urine calcium excretion greater than 4 mg/kg per day in the absence of hypercalcemia and with no other identifiable cause. Hyperuricosuria was defined as uric acid excretion greater than 815 mg/d/1.73 m^2 of body surface area. Nutcracker syndrome (NCS) was diagnosed when the peak velocity (PV) of the left renal vein was at least 4.1 (the calculated cutoff level of the aortomesenteric PV2/hilar PV1 ratio).[6]

Grouping

All 351 patients were divided into two groups according to the presence of macrohematuria and/or proteinuria: 215 patients with asymptomatic isolated microhematuria (AIMH), proteinuria <0.1 g/day and no macrohematuria; and 136 patients with persistent asymptomatic microhematuria, recurrent macrohematuria and/or proteinuria (AMHP), recurrent macrohematuria and/or moderate proteinuria (0.1-0.25 g/day).

Ultrasound-guided kidney biopsy

The indications for kidney biopsy in children with persistent asymptomatic isolated hematuria were as follows: (1) a history of asymptomatic isolated hematuria persisting more than 6 months; (2) patient preference; (3) parental anxiety; (4) positive family history; and (5) exclusion of non-glomerular diseases, such as CAKUT, urinary tract infections, trauma, drug-induced hematuria, idiopathic hypercalciuria, hyperuricosuria, or urolithiasis.

All patients underwent renal biopsy using ultrasonic guidance. Local anesthesia was adopted for older children, and ketamine or propofol dissociative anesthesia was used for infants or young children. Tissue samples were assessed by light microscopy using hematoxin eosin, periodic acid schiff, periodic acid methenamine, or masson staining, indirect immunofluorescence by staining with antibodies against IgG, IgA, IgM, C3, C4, Fib, type-IV collagen and HBsAg, and electron microscopy. The pathologic features of IgA nephropathy were classified into five histologic grades according to Lee's classification.[7]

Adverse renal events

Adverse renal events were defined as follows: development of significant proteinuria (>0.5 g/day) on two consecutive occasions; development of hypertension; and impaired renal function characterized by a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more.[8] Hypertension was defined as blood pressure above the 95th percentile for age according to data from the Task Force Report on High Blood Pressure in Children and Adolescents.[9] Patients developed with at least one of the 3 events will be defined as presenting adverse renal events.

Follow-up

All individuals were followed for 2-10 years. Routine examinations included routine urine testing, urine β2-microglobulin testing after 1995, 24-hour urine protein excretion, serum creatinine and/or estimated GFR (eGFR, calculated by the Schwartz formula),[10] B ultrasound for both kidneys and mental and physical development.

Statistical analysis

The Kaplan-Meier plot using the log-rank test was used to compare the incidence of adverse renal events between the two groups. The Chi-square test and logistic regression analysis were used to compare the difference of clinical events affecting the happening of adverse renal event and long-term prognosis between the two groups. SPSS 16.0 was used for statistical analysis. A *P* value less than 0.05 indicated a statistically significant difference.

Results

Demographic characteristics

The mean age of the patients at presentation was 9.5 years (2.1-16.8 years). The study included 219 male and 132 female patients (male:female=1.7:1). The median follow-up period was 3.7 years (2.2-10.2 years) (Table 1).

Pathology

Samples were successfully obtained in all cases by B ultrasound-guided renal biopsy (>10 glomeruli per sample). Histological findings revealed 191 patients (54.4%) with normal biopsies/minor lesions, 114 (32.5%) with IgA nephropathy (IgAN), 9 (2.6%) with focal segmental proliferative glomerulonephritis (FPGN), 21 (6.0%) with mesangial proliferative glomerulonephritis (MsPGN), 8 (2.3%) with thin basement membrane nephropathy (TBMN), 4 (1.1%) with Alport syndrome (Alport's), 1 (0.3%) with IgM nephropathy, and 3 (0.9%) with interstitial nephritis. The pathological patterns of both groups are shown in Table 2.

The potential causes of hematuria with a normal renal biopsy may include NCS, calculi <5 mm (too small to be detected by routine assessment of ultrasonography or plain abdominal radiography) and infection-related glomerulonephritis (neither typical acute post-streptococcal glomerulonephritis nor HBV-related glomerulonephritis). Shin et al[6] reported that NCS was present in 60 (40%) of 149 children in whom no other explanations for hematuria present. In another study about the non-glomerular hematuria conducted in our hospital, the percentage of patients with crystalluria was 35.4%, and the percentage of patients with NCS was 19.2% (unpublished data).

Familial history

Several first-degree relatives of 39 patients were identified as having a history of hematuria or end-stage renal disease (ESRD). Among them, 22 were classified in the AIMH group, and 17 in the AMHP group (Table 3).

Treatment strategy

None of the patients received any specific treatment prior to renal biopsy, with the exception of patients with gross hematuria who underwent symptomatic treatment with hydration and urine alkalization to prevent the development of acute tubular necrosis, intraluminal obstructive red blood cell casts and acute kidney injury. After renal biopsy, patients with normal biopsies or minor lesions received no specific treatment except for routine follow-up. Nine patients with IgAN underwent tonsillectomy, and hematuria was mitigated

Table 1. Clinical features of 351 children with persistent asymptomatic isolated hematuria

Clinical features	AIMH	AMHP	*P* value
n	215	136	
Mean age during renal biopsy, y	9.2±4.7	9.9±3.9	0.146
Male/female	139/80	80/56	0.381
Family history of renal disease	22	17	0.510
Baseline proteinuria, mg/24 h	85.3±34.9	226.4±128.5	<0.001
eGFR (Schwartz formula)	102.3±28.8	95.5±26.2	0.055
Baseline serum urate level, μmol/L	355.6±148.9	331.7±169.5	0.169
Elevated IgA serum concentration	56	52	0.016
Follow-up, y	3.5±2.1	3.7±2.9	0.079
Complete resolution of hematuria	71	32	0.057
Persistent hematuria without adverse events	131	73	0.180*
Hypertension	3	13	
Significant proteinuria (>500 mg/d)	7	12	<0.001†
Impaired renal function	3	6	

AIMH: asymptomatic isolated microhematuria; AMHP: persistent asymptomatic microhematuria with recurrent macrohematuria and/or proteinuria; eGFR: estimated glomerular filtration rate. *: the Chi-square test, χ^2=1.801; †: The incidence of hypertension, significant proteinuria and impaired renal function (combined) was compared between the two groups using a Kaplan-Meier method with the log-rank test, χ^2=14.796, all *P*<0.001 (see also Fig). By logistic regression analysis, there is no significant correlation between the happening of adverse renal events and eGFR, baseline serum urate, gender or the mean age during renal biopsy, except for baseline proteinuria.

Table 3. Positive family history of patients with AIMH or AMHP

Patients	First-degree relatives	Second-degree relatives	Total
AIMH	15	10	22*
AMHP	11	8	17*

*: Three patients with asymptomatic isolated microhematuria (AIMH) and two patients with persistent asymptomatic microhematuria with recurrent macrohematuria and/or proteinuria (AMHP) had positive family histories in both first- and second-degree relatives.

Table 2. Renal biopsy results of patients with AIMH or AMHP

Patients	*n*	IgAN	Nnormal biopsies/minor lesions	MsPGN	TBMN	Alport's	FPGN	Others
With microhematuria	215	35	152	11	7	3	5	2
With macrohematuria	136	79	39	10	1	1	4	2
Total	351	114	191	21	8	4	9	4

IgAN: IgA nephropathy; MsPGN: mesangial proliferative glomerulonephritis; TBMN: thin basement membrane nephropathy; Alport's: Alport syndrome; FPGN: focal proliferative glomerulonephritis; AIMH: asymptomatic isolated microhematuria; AMHP: persistent asymptomatic microhematuria with recurrent macrohematuria and/or proteinuria.

in two of them. Three patients with interstitial nephritis were treated with 1 mg/kg per day prednisone for three months, and hematuria resolved in all of them.

Follow-up

The follow-up period in the AIMH group was 3.5±2.1 years, and that in the AMHP group was 3.7±2.9 years. Hematuria completely resolved in 71 patients with AIMH and 32 patients with AMHP (χ^2=3.621, P=0.057). Persistent hematuria without adverse events was observed in 131 patients with AIMH and 73 with AMHP (χ^2=1.801, P=0.180). Sixteen patients developed hypertension (3 in AIMH and 13 in AMHP), 19 developed significant proteinuria (>0.5 g/day) (7 in AIMH and 12 in AMHP) and 9 developed impaired renal function (3 in AIMH and 6 in AMHP). To compare the incidence of adverse renal events between the two groups, a Kaplan-Meier plot using the log-rank test was constructed. The plot revealed a significant difference in the occurrence of adverse renal events between patients with AIMH and those with AMHP (χ^2=14.796, P<0.001) (Table 1 & Fig).

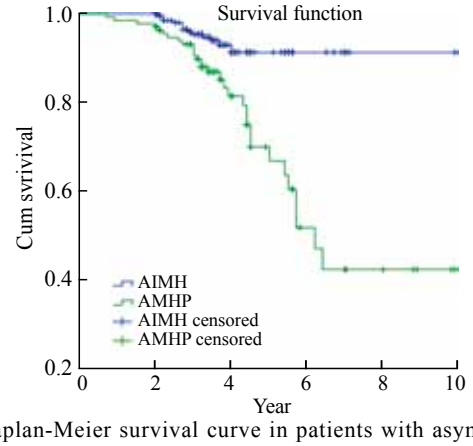

Fig. Kaplan-Meier survival curve in patients with asymptomatic isolated microhematuria (AIMH) or persistent asymptomatic microhematuria, recurrent macrohematuria and/or proteinuria (AMHP) determined using the log-rank test.

Discussion

Persistent asymptomatic isolated microscopic hematuria is frequently encountered in clinical practice in China because of economic development and enhanced health awareness, but studies to support current recommendations regarding the evaluation and management of persistent AIMH are long overdue.[8] The literature does not provide clear and sufficient guidelines for how to approach and counsel a child with asymptomatic isolated microscopic hematuria.[11]

Histopathologically, IgAN, normal biopsies, minor lesions and non-IgA MsPGN accounted for the majority of patterns in asymptomatic isolated hematuria, followed by TBMN, Alport's, membranous proliferative glomerulonephritis and FPGN. The histopathological patterns observed were quite similar to those of studies published domestically. However, the histopathological diagnoses were different between the AIMH and AMHP groups. The most common findings in the AIMH group were normal biopsies or minor lesions, whereas IgAN was the most common finding in the AMHP group, which suggests a positive association between the severity of clinical features and the histopathological pattern. Therefore, macrohematuria and/or proteinuria may indicate relatively severe histopathological results.

To our knowledge, this is the first study to evaluate the histopathological pattern and long-term prognosis of children with persistent asymptomatic microscopic hematuria with or without macrohematuria and/or proteinuria. Many studies have typically focused on patients with persistent asymptomatic microscopic hematuria without macrohematuria, whereas those from China often include patients with persistent asymptomatic microscopic hematuria complicated with

Table 4. Comparison of pathological diagnoses in patients with AIMH or AMHP in different studies

	Publishing year	*n*	IgAN	Normal biopsies/minor lesion	MsPGN	TBMN	Alport's	FPGN	Others
With isolated microscopic hematuria									
Chow[8]	2004	28	8	11	-	4	5	-	-
Shen[12]	2007	216	97	23	19	56	-	9	12
Kovacević[13]	2008	62	22	19	15	3	-	-	3
Kim[14]	2009	156	52	34	37	20	-	-	-
Present study	2013	215	35	152	11	7	3	5	2
With isolated microscopic hematuria and recurrent macrohematuria									
Cai[15]	2006	128	52	18	31	Total 27 cases			
Wan[16]	2007	310	163	56	52	1	-	-	38
Chen[17]	2010	251	52	155	16	17	-	5	6
Present study	2013	136	79	39	10	1	1	4	2

IgAN: IgA nephropathy; MsPGN: mesangial proliferative glomerulonephritis; TBMN: thin basement membrane nephropathy; Alport's: Alport syndrome; FPGN: focal proliferative glomerulonephritis; AIMH: asymptomatic isolated microhematuria; AMHP: persistent asymptomatic microhematuria, recurrent macrohematuria and/or proteinuria.

or without macrohematuria (Table 4). The inclusion criterion for proteinuria in individuals with persistent asymptomatic isolated microscopic hematuria can also vary across studies. Parmar[18] stated that in pure isolated microscopic hematuria, the urine protein excretion rate should be <0.1 g/day, whereas Chow et al[8] included patients with microscopic hematuria and minimal proteinuria (0.3±0.1 g/day). As expected, most of the patients in the latter group experienced adverse events because of the higher baseline protein excretion rate.

Additionally, the incidence of adverse renal events differed significantly between the two groups in the present study. Approximately 22.8% (31/136) of patients developed hypertension, significant proteinuria or impaired renal function in the AMHP group, whereas only 6.0% (13/215) of patients in the AIMH group experienced similar events, which indicates that macrohematuria and/or proteinuria, including even moderate proteinuria (0.1-0.25 g/day, according to most literature), are important risk factors and prognostic markers for adverse renal events and the development of glomerular nephropathy. With a median follow-up of 3.6 years, the present study raises the concern of potentially progressive renal diseases or hypertension in patients with isolated microhematuria and suggests that this condition may not be as benign as thought previously.

The relationship between microhematuria and negative renal outcomes has been reported in several studies. Vivante et al[19] reported that over 21.88±6.74 years of follow-up, ESRD developed in 0.70% of individuals with persistent AIMH (26/3690 cases) but in only 0.045% of patients without persistent AIMH (539/1 199 936 cases), which suggests that persistent AIMH confers an increased risk for ESRD (hazard ratio=18.5, 95% CI=12.4-27.6). In contrast, the fraction of treated ESRD cases attributed to microscopic hematuria is 4.3% (95% CI=2.9%-6.4%).

A recent study[4] has reported an association between glomerular macroscopic hematuria and AKI. Praga et al[20] reported 29 episodes of macroscopic hematuria in 21 patients with IgAN in a 3-year period. A disruption of renal function was observed in 11 episodes. The histological survey revealed that the decrease in renal function was correlated closely with the presence of red blood cell casts in as much as 50% of the tubular lumen and with findings of tubular necrosis. The authors concluded that worsening renal function can frequently be observed during episodes of macroscopic hematuria. Tubular damage and obstruction by red blood cell casts may play a significant role in the pathogenesis of this complication. Kveder et al[21] also reported that during the period from 1990 to 2005, 7 of the 584 adult patients with IgA nephropathy (1.2%) fulfilled the criteria for macroscopic hematuria-induced AKI. Although all the patients evaluated in both studies recovered their kidney function after the episodes of macroscopic hematuria, Gutiérrez et al[22] and Moreno et al[4] stated that 25% to 27% of patients with macroscopic hematuria-associated AKI do not recover baseline renal function. These studies introduced the hypothesis, supported by the present study, that microscopic hematuria and especially macroscopic hematuria complicated with proteinuria may represent important risk factors for the development of chronic kidney disease.

In the present study, normal biopsies and minor abnormalities were more frequently observed in the AIMH patients, whereas IgA nephropathy and adverse renal events were more frequently observed in the AMHP patients. Microscopic hematuria, especially microscopic hematuria accompanied by macroscopic hematuria and proteinuria, may be an important risk factor for the development of chronic kidney disease in children. The results from the present study imply that macroscopic hematuria and proteinuria are the important indicators for renal biopsy and early intervention.

Acknowledgements

We thank all the patients for participating in this study.

Funding: This project was supported by the National Natural Science Foundation of China (Grant No. 81270792, 81070561 & 81170664), the Research Fund for the Doctoral Program of Higher Education of China (20120101110018), Zhejiang Provincial Healthy Science Foundation of China (WKJ2010-2-014, 2012KYA119).

Ethical approval: This study was approved by Clinical Research Ethics Committee of the Children Hospital of Zhejiang University School of Medicine.

Competing interest: No competing interest declared.

Contributors: Xia YH had full access to all of the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis. Xia YH, Liu AM and Mao JH were responsible for study conception and design. Feng CY, Xia YH, Wang WJ, Jin X, Fu HD, Wang X, Shen HJ and Qian GL were responsible for data collection, analysis and interpretation. Feng CY and Xia YH contributed to the manuscript writing and modification.

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Received December 14, 2012
Accepted after revision April 23, 2013