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Clinicopathological Analysis of 155 Patients with Persistent Isolated Hematuria

Rong-rong Li¹, Hang Li^{2*}, Yu-bin Wen², Qing-yuan Huang²,
Lin Duan², and Yan Li²

¹Department of Clinical Nutrition, ²Department of Nephrology, Peking Union
Medical College Hospital, Chinese Academy of Medical Sciences & Peking
Union Medical College, Beijing 100730, China

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Objectives To reveal etiologies of persistent isolated hematuria (PIH) through ultrastructural pathological examination, to disclose clinicopathological correlation in cases with PIH, and to summarize appropriate management of patients with PIH.

Methods we retrospectively studied 155 PIH patients receiving renal biopsy between January, 2003 and December, 2008 in Peking Union Medical College Hospital. All the clinical data and follow-up result were analyzed.

Results All subjects included 38 children and 117 adults, with mean age of 11.38 ± 3.25 years for children and 35.17 ± 8.44 years for adults. Thin basement membrane nephropathy (TBMN) was the most common pathology (55.3% of children and 49.6% of adults), followed by IgA nephropathy (18.4% of children and 32.5% of adults, mainly grade 2-3) and mesangial proliferative glomerulonephritis (MsPGN) without IgA deposition (13.2% of children and 12.8% of adults). Besides, Alport syndrome (2.6% of children) and membrane nephropathy (2.6% of children and 0.9% of adults) were demonstrated as other causes of PIH. Elevated mean arterial pressure or protein excretion rate, as well as episodic macrohematuria, indicated higher risk for MsPGN rather than TBMN. On the other hand, severity of microhematuria was irrelevant to pathological types of PIH. Totally, 86 patients were followed up and 37 cases therein stayed on track for long term (mean duration 41.11 ± 28.92 months, range 8-113 months). Most cases had benign clinical course except 3 cases with TBMN, 5 cases with IgA nephropathy, 1 case with MsPGN (without IgA deposition), and 1 case with Alport syndrome, who developed hypertension or proteinuria. All of them were administered timely intervention.

Conclusions Close follow-up should be required as the primary management for PIH. Equally important is careful monitoring for early identification of undesirable predictors; while renal biopsy and other timely intervention are warranted if there is hypertension, significant proteinuria or renal impairment.

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PERSISTENT isolated hematuria (PIH) is a common urinary abnormality frequently detected in health examination by routine urinalysis and phase-contrast microscopic examination, indicating dysmorphic erythrocytes originating from glomerules. The patients barely had other clinical symptoms including hypertension, renal insufficiency, proteinuria, or any other extrarenal causes of hematuria.¹ As a prevalent condition, PIH has been demonstrated to be present in 0.1% to 2.7% of adolescents and adults,^{2, 3} while in 0.008% to 2.0% of children by many large-sample studies.⁴⁻¹⁰

Despite the frequency of PIH, evidence-based guidelines have been lacking for its proper evaluation, management and prognosis. Some nephrologists consider PIH as an early sign of chronic renal disease for which renal biopsy is necessary for early detection and treatment to reduce risk of end-stage renal disease.^{11, 12} While others assert that PIH has a benign course so that it will be more rational to take a "wait and watch" approach rather than perform renal biopsy.¹³ We conducted a retrospective study to analyze the clinical and pathological features of PIH, and provide practical implication of management for such patients.

PATIENTS AND METHODS

Patients

From January, 2003 to December, 2008, 4360 patients underwent renal biopsy at the Department of Nephrology in Peking Union Medical College Hospital (PUMCH), which included 155 consecutive individuals (3.56%) presenting with PIH. The diagnosis of PIH was defined as: (1) an erythrocyte excretion rate ≥ 3 erythrocytes per high-power field (HPF) revealing dysmorphic red blood cells from centrifuged urine obtained on 3 or more separate occasions over 4 or more weeks; (2) urinary protein excretion < 0.3 g/24 h prior to renal biopsy; (3) serum creatinine values within the normal range (≤ 132.6 $\mu\text{mol/L}$) and the estimated glomerular filtration rate ≥ 60 ml/(min $\cdot 1.73$ m ^{2}) by Modification of Diet in Renal Disease (MDRD) equation; (4) normal blood pressure (systolic pressure < 140 mm Hg and diastolic pressure < 90 mm Hg). All the clinical and pathological data (including light microscopy, immunofluorescence, and electron microscopy results) were intact and complete.

Patients with PIH were divided into 4 groups according to various clinical features: (1) persistent isolated microscopic hematuria with family history of hematuria, nephropathy or renal failure (PIMH+FH); (2) persistent isolated microscopic hematuria with episodic gross hematuria (PIMH+GH); (3) persistent isolated microscopic

hematuria with episodic gross hematuria as well as positive family history (PIMH+FH+GH); (4) persistent isolated microscopic hematuria as the sole manifestation (PIMH).

Fifty-four patients (including 14 children and 40 adults) received quantification of urinary erythrocyte count in urinalysis. The severity of hematuria was defined as three levels: 3-5/HPF, 6-10/HPF, and > 10 /HPF.

All the PIH patients were scheduled for periodic follow-up visits to nephrologists. Urinalysis was recommended to be performed at 1- to 3-month intervals, and assessment of blood pressure and renal function was also required at follow-up visits.

Renal pathology evaluation

Renal biopsies were obtained through a standard percutaneous technique. Tissue containing more than 10 glomeruli was fixed and embedded into paraffin sections for light microscopy, immunofluorescence, and electron microscopy examination. In electron microscopic examination, ultra-structure of renal tissue as well as electron-dense immune deposits were reviewed and photographed by JEOL-1010 transmission electron microscope (Japan Electron Optics Laboratory Co., Ltd.). The diagnosis of mesangial proliferative glomerulonephritis (MsPGN) is made when light microscopy reveals an increase in mesangial matrix, hypercellularity and other glomerular lesions including focal necrosis, segmental scarring, and crescents in Bowman's space; while electron microscopy shows electron-dense material mainly in the mesangial and paramesangial areas corresponding to immune deposits on immunofluorescence microscopy. Predominance of IgA deposits in the glomerular mesangium is the diagnostic hallmark of IgA nephropathy (IgAN).¹⁴ Features of IgAN on light microscopy is classified according to Lee's histological grading system¹⁵ as follows: grade I, mostly normal glomeruli; grade II, $< 50\%$ glomeruli show segmental mesangial hypercellularity and sclerosis; grade III, diffuse mesangial proliferation with occasional adhesions and small crescents; grade IV, diffuse marked mesangial proliferation and $\leq 45\%$ glomeruli having crescents with frequent segmental and global sclerosis; grade V, similar to IV but more severe with $> 45\%$ glomeruli showing crescents. Thin basement membrane nephropathy (TBMN) was diagnosed when diffuse thinning of the glomerular basement membrane (GBM, GBM thickness less than 200 nm¹⁶ for children or less than 280 nm for adults) existed in the majority of capillary loops with at least 80% of the GBM involved in individual capillaries.

Statistical analysis

Data were analyzed by SPSS 16.0 statistical software.

Continuous variables were expressed as means $\pm$ SD. Normally distributed data was compared with analysis of variance (ANOVA) or *t* test; while χ^2 test was used for comparison of proportions and ratios. A *P*-value less than 0.05 was considered to be statistically significant.

RESULTS

Demographic and clinical features

A total of 38 children and 117 adults were enrolled in the study. The age range was 6 to 57 years (11.38 $\pm$ 3.25 years and 35.17 $\pm$ 8.44 years for children and adults, respectively). In paediatric patients, the female to male ratio was 1.11 to 1 (female/male: 20/18), while the ratio was 3.07 to 1 (female/male: 89/29) for adults. The clinical manifestation varied. Eight (21.1%) children and 36 (30.8%) adults had recurrent bouts of gross hematuria for more than once. Nine (23.6%) children and 15 (12.8%) adults had positive family history of hematuria, nephropathies or renal failure in close relatives. In addition, nutcracker phenomenon was found by ultrasound in 4 (10.5%) children and 12 (10.2%) adults.

Pathology distribution

TBMN was the most frequent pathological diagnosis, accounting for 55.3% and 49.6% of paediatric and adult patients, respectively. Next came IgAN, found in 18.4% of children and 32.5% of adults, mainly grade 2-3, followed by MsPGN without IgA deposition (accounting for 13.2% of children and 12.8% of adults). There was no significant difference between paediatric and adult patients in distribution of pathological patterns (χ^2 test, *P*=0.078, Table 1).

Clinicopathological features of PIH

Children with TBMN had lower quantitative protein excretion rates than those with IgAN alone or MsPGN combined with TBMN; while adults with TBMN had lower mean arterial pressure (MAP) than those with IgAN, other MsPGN without IgA deposition and MsPGN combined with TBMN (all *P*<0.05, Tables 2, 3). It is noteworthy that adults with episodic macrohematuria had higher risk of IgAN (52.6%) than TBMN (15.6%, *P*=0.000, Table 3). On the other hand, family histories of hematuria, nephropathy or renal failure were uncorrelated with pathological changes (all *P*>0.05, Tables 2, 3). In addition, 2 children and 6 adults diagnosed with TBMN had family history of nephropathies or renal failure, for whom ophthalmologic examinations and hearing tests were performed and detected no abnormality.

Pathological distribution in patients with different clinical features

χ^2 test showed the pathological distribution of the PIMH+GH group was significantly different from the PIMH+FH group (*P*=0.002) and PIMH group (*P*=0.000). MsPGN (mainly IgAN) accounted for the most common pathology in the PIMH+GH group, while hereditary nephritis (mainly TBMN) predominated in both the PIMH+FH group and PIMH group (Table 4).

Relationship between pathological pattern and urinary erythrocyte count

There was no significant correlation between pathological changes and severity of hematuria for children (*P*=0.425) as well as for adults (*P*=0.151, Table 5).

Table 1 Pathological distribution of 155 patients with persistent isolated hematuria revealed by renal biopsy

Pathological types	Children		Adult		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
TBMN	21	55.3	58	49.6	79	51.0
TBMN combined with MsPGN	2	5.3	4	3.4	6	3.9
Alport syndrome	1	2.6	0	0	1	0.6
IgAN	7	18.4	38	32.5	45	29.0
Grade 2	6	15.8	16	13.7	22	14.2
Grade 3	1	2.6	21	17.9	22	14.2
Grade 4	0	0	1	0.9	1	0.6
MsPGN without IgA deposition	5	13.2	15	12.8	20	12.9
IgM nephropathy	0	0	2	1.7	2	1.3
MsPGN with negative immunofluorescence	5	13.2	13 [#]	11.1	18	11.6
MN	1	2.6	1	0.9	2	1.3
Normal	1	2.6	1	0.9	2	1.3
Total	38	100.0	117	100.0	155	100.0

TBMN: thin basement membrane nephropathy; MsPGN: mesangial proliferative glomerulonephritis; IgAN: IgA nephropathy; MN: membrane nephropathy; [#] two patients had concurrent tubulointerstitial lesion.

Table 2. Clinicopathological features of 38 children with persistent isolated hematuria

Pathological types	<i>n</i>	Age [§] (yrs)	MAP [§] (mm Hg)	24h Upro [§] (g/24 h)	sCr [§] (μmol/L)	BUN [§] (mmol/L)	Sex (Female/Male)
TBMN	21	9.74±2.73	73.32± 9.15	0.04±0.06* [#]	57.50± 8.80	4.22±0.88	14/7
IgAN	7	13.14±2.19	72.38± 9.76	0.17±0.09	65.40± 9.70	4.34±1.37	1/6
Other MsPGN without IgA deposition	5	13.40±3.21	82.00±12.16	0.10±0.08	69.00±20.30	4.62±0.77	3/2
TBMN combined with MsPGN	2	12.00±5.66	75.83± 3.56	0.21±0.13	58.30± 0.90	4.08±1.38	2/0
Others (Alport syndrome, MN, normal)	3	15.00±1.00	73.33± 3.33	0.14±0.13	76.00± 1.80	4.82±1.74	0/3

Pathological types	Episodic macrohematuria (<i>n</i>)	Nutcracker Phenomenon (<i>n</i>)	Family history (<i>n</i>)			Suspected autoimmune disease (<i>n</i>)	Chronic hepatitis (<i>n</i>)
			Hematuria	Nephropathy	Renal failure		
TBMN	3	3	2	2	0	1	0
IgAN	3	0	0	1	0	0	0
Other MsPGN without IgA deposition	2	1	2	0	0	2	0
TBMN combined with MsPGN	0	0	0	0	0	1	0
Others (Alport syndrome, MN, normal)	0	0	0	1	1	0	0

§: Plus-minus values are means±SD.

MAP: mean arterial pressure; Upro: urinary protein excretion rate; sCr: serum creatinine; BUN: blood urea nitrogen.

P*<0.05 compared with patients with IgAN; [#]*P*<0.05 compared with patients with TBMN combined with MsPGN.Table 3.** Clinicopathological features of 117 adults with persistent isolated hematuria

Pathological types	<i>n</i>	Age [§] (yrs)	MAP [§] (mm Hg)	24h Upro [§] (g/24h)	sCr [§] (μmol/L)	BUN [§] (mmol/L)	Sex (Female/ Male)
TBMN	58	35.29±7.28	82.76±7.83	0.10±0.09	76.90±11.50	4.58±1.38	43/15
IgAN	38	32.32±9.21	86.54±7.36*	0.14±0.10	77.80±11.50	4.68±1.19	29/9
Other MsPGN without IgA deposition	15	37.13±7.59	88.22±5.21*	0.10±0.13	82.20±12.40	4.39±1.18	11/4
TBMN combined with MsPGN	4	43.75±5.97	92.50±8.77*	0.12±0.11	67.20±10.60	4.20±0.78	4/0
Others (Alport syndrome, MN, normal)	2	47.67±7.77	87.78±7.70*	0.22±0.03	70.70±31.80	5.45±2.18	1/1

Pathological types	Episodic macrohematuria (<i>n</i>)	Nutcracker phenomenon (<i>n</i>)	Family history (<i>n</i>)			Suspected autoimmune disease (<i>n</i>)	Chronic hepatitis (<i>n</i>)
			Hematuria	Nephropathy	Renal failure		
TBMN	9 [#]	9	3	3	3	17	3
IgAN	20	1	1	1	1	10	1
Other MsPGN without IgA deposition	4	1	0	0	1	1	2
TBMN combined with MsPGN	1	0	2	0	0	1	0
Others (Alport syndrome, MN, normal)	1	1	0	0	0	1	0

§: Plus-minus values are means±SD.

**P*<0.05 compared with patients with TBMN; [#]*P*<0.05 compared with patients with IgAN.

Table 4. Comparisons of pathological distribution among the four groups (%)

Groups	<i>n</i>	TBMN	Alport syndrome	IgAN	MsPGN without IgA deposition	TBMN with concomitant MsPGN	MN	Normal
PIMH+FH*	19	11(57.9)	1(5.3)	3(15.8)	2(10.5)	1(5.3)	1(5.3)	0
PIMH+GH	34	7(20.6)	0	21(61.8)	5(14.7)	0	1(2.9)	0
PIMH+FH+GH	6	3(50.0)	0	1(16.7)	1(16.7)	1(16.7)	0	0
PIMH*	96	58(60.4)	0	20(20.8)	12(12.5)	4(4.2)	0	2(2.1)

**P*<0.01 compared with the PIMH+GH group.

Table 5. Correlation of pathological presentation with severity of hematuria (*n*)

Urinary erythrocyte count (/high-power field)	TBMN		IgAN		MsPGN without IgA deposition		TBMN combined with MsPGN		Others (Alport syndrome, MN, normal)	
	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
3-5	0	1	0	0	0	0	0	0	1	0
6-10	0	1	0	1	0	0	0	0	0	1
>10	6	16	3	12	2	8	1	0	1	0
Total	6	18	3	13	2	8	1	0	2	1

Follow-up

A total of 69 patients were transferred to local hospitals for convenience sake, while 86 patients were followed up in PUMCH. And 49 of 86 patients stayed on track in PUMCH for less than 6 months and afterwards rescheduled follow-up visits at other hospitals, including 31 cases with TBMN, 11 cases with IgAN, 4 cases with MsPGN (without IgA deposition), 2 cases with membrane nephropathy and 1 case with normal pathology. Although microscopic hematuria was persistently reported, none of the patients developed proteinuria, hypertension or renal insufficiency during their follow-up in PUMCH.

Besides, 37 cases (33 adults and 4 children) were followed up in PUMCH for more than 6 months, including 20 cases with TBMN, 13 cases with IgAN, 1 case with Alport syndrome, 1 case with MsPGN (without IgA deposition) and 2 case with normal pathologies. The mean duration of follow-up was 41.11±28.92 (range 8-113) months, and 15 patients therein were kept track of for over 60 (mean 84.55±16.61, range 60-113) months. Microscopic hematuria persisted in all the 37 patients during the entire follow-up; moreover, hypertension or proteinuria was identified in 10 cases, all with renal function spared. The subjects comprised 3 cases with TBMN, 5 cases with IgAN, 1 cases with MsPGN (without IgA deposition), and 1 case with Alport syndrome. Herein, the 3 TBMN patients included 1 female child (13 years old) and 2 female adults (21 and 33 years old), with the child and 1 adult having family history of uremia. Angiotensin-converting enzyme inhibitors or angiotensin-

receptor blocker were prescribed to the 10 patients in time to manage hypertensiton and reduce proteinuria, while immunosuppressants were administered to 2 cases with IgAN.

DISCUSSION

PIH is a frequent condition in clinical practice. In this study, TBMN served as its most common cause in children (55.3%) and adults (49.6%), followed by IgAN and MsPGN without IgA depositon. The results were roughly in line with those reported previously in UK (1998),¹⁷ New Zeland (1998)¹⁸ and China (2012).¹⁹ However, a Korean study on adults in 2009²⁰ and a Chinese study on peadiatric patients in Hangzhou in 2013²¹ revealed different results: IgAN was found to be the leading pathology (12.8%) while TBMN accounted for a much smaller proportion of 2.3%. These discrepancies may be due to differences of sample sizes, frequency of urinalysis screening in local residents, indications for renal biopsy, and availability of electron microscopy among different regions as well as geographical and ethnic differences.^{20, 22}

As the two most common etiologies of PIH, TBMN and MsPGN (mainly IgAN) differ in either clinical manifestation or prognosis. Our results reveal more obvious proteinuria in children with MsPGN as well as higher MAP in adults with MsPGN, as compared with those with TBMN. It is in accordance with other previous studies.²³ Although these parameters were within normal range in our study, a

tendency of elevated MAP or protein excretion rate is indicative of MsPGN especially IgAN.

As another significant indicator, presence of episodic gross hematuria signifies high risk of MsPGN and a potentially undesirable outcome. Other studies have reported the association between glomerular macroscopic hematuria and development of acute kidney injury with tubular cell damage.²⁴ There is also increasing evidence to support the negative effect of episodic macrohematuria on long-term renal function, especially in the context of IgAN.^{21, 25} On the other hand, no correlation is found between microhematuria levels and pathological changes. Thus severity of microhematuria might be neither parallel with glomerular lesion nor indicative of prognosis of PIH.

In our study, there is no significant difference among PIMH+FH group, PIMH+FH+GH group, and PIMH group in pathology distribution. Accordingly, for patients with PIH, presence of family history cannot serve as the sole discriminator to differentiate TBMN from IgAN. In previous researches, familial clustering has been reported in 10%-15% of cases of IgAN in Europe and USA,²⁶ while familial microhematuria is common in patients with TBMN.²⁷ However, familial forms of IgAN are frequently underrecognized due to overlooked urinary abnormalities in affected family members;²⁶ whereas a previous investigation revealed one-third of patients with TBMN failed to provide positive family histories.²³ Besides, even if the heritable hematuric condition is present, it may result from a genetically heterogeneous group of monogenic diseases except for TBMN, involving mutation of collagen IV genes COL4A3/A4/A5, the FN1 gene, or CFHR5 gene.²⁷ Overall, the presence of a family history of proteinuria or renal insufficiency indicates predisposition to more severe disease with unfavourable prognosis.²⁷ In a nutshell, evaluation of one's family history should be in combination with other clinical information. And it is advisable to popularize urinalysis screening in local residents, raise public concern for hematuria and other nephrotic presentations, and detect full details of family members's history. In some cases with equivocal findings, molecular analysis might be required to establish the diagnosis.

Another surprising finding is that 2 children and 6 adults, with pathologies consistent with TBMN by electronic microscopy, had family history of nephropathy or renal failure. The clinical feature is opposite to the fact that TBMN is usually characterized by familial isolated hematuria. Moreover, 3 patients (including 1 adult and 1 child with family history of uremia) initially diagnosed with TBMN gradually developed proteinuria and hypertension during long-term follow-up. To account for unfavourable progres-

sion of symptoms, risk of Alport syndrome might be considered in these cases when other renal diseases were excluded. As an autosomal dominant genetic disease, TBMN is caused by heterozygous mutations in the collagen type IV genes (COL4A3/A4), leading to uniformly thinned GBM. Given its benign clinical course, TBMN is also named 'benign familial hematuria'. In contrast, Alport syndrome is a genetically heterogeneous condition with unfavorable outcome, attributable to various mutations in the COL4A5 gene located on the X chromosome, or COL4A3/A4 locus on chromosome 2.²⁸ Typical ultrastructural changes of Alport syndrome include splitting and lamellation of GBM with loss of normal lamina densa, alternating zones of thinning and thickening of GBM, and an irregular outer contour of the GBM.²⁸ However, some patients with Alport syndrome, especially heterozygous carriers of X-linked Alport syndrome, autosomal recessive Alport syndrome, and some cases in early stages of X-linked Alport syndrome, have predominantly thin GBM resembling changes seen in TBMN. On this account, it is essential to schedule close follow-up for TBMN cases, and evaluate clinical manifestations in addition to electron microscopy for confirmation or exclusion of atypical Alport syndrome. Ophthalmologic examinations, hearing tests, combinations of electromicroscopy and immunohistologic test for $\alpha 3$ (IV) and $\alpha 5$ (IV), or even DNA analysis might be undertaken if necessary.

In our research, 1 (0.9%) adult patient was diagnosed with normal biopsy, and concomitant nutcracker phenomenon (NCP) was identified by Doppler ultrasound. NCP is also known as left renal vein entrapment, occurring in the setting of compression of the left renal vein between superior mesenteric artery and abdominal aorta. As its common manifestation, hematuria is considered to be characterized by nonglomerular isomorphic erythrocytes,²⁹ whereas in some cases dysmorphic microhematuria also results from NCP.³⁰ Hence, NCP should be considered as a possible etiology of PIH especially when a normal biopsy rules out other renal diseases.

There still has been controversy on necessity of renal biopsy on patients with PIH. Considering favorable outcome of PIH under most circumstances, we assert that close follow-up should be required as the primary management. Equally important is careful monitoring for early identification of undesirable predictors; while renal biopsy and other timely therapeutic intervention are warranted if there is hypertension, significant proteinuria or renal impairment. Even if PIH patients have more than 30% of risk for MsPGN (mainly IgAN) according to our pathological examination, mild pathological lesions (mainly glomerular grades 2 and

3) seldom require aggressive treatment. Besides, Alport syndrome, another condition contributing to end stage renal disease in later life, also accounts for less than 1% of causes of PIH. However, in most cases of Alport syndrome with hematuria alone, no special treatment except for careful follow-up for signs of progression is encouraged. Extensive evaluation including renal biopsy, as well as therapeutic intervention might be performed at onset of hearing loss, lenticonus, proteinuria, hypertension and renal impairment.

Currently, there is no consensus on management of PIH.^{21, 31} More studies with larger sample sizes and long-term follow up are required.

In conclusion, TBMN and MsPGN (mainly IgAN) accounts for the majority of histopathological patterns in patients with PIH. Elevated MAP or protein excretion rate, as well as episodic macrohematuria, indicate higher risk of MsPGN rather than TBMN. Although intervention of PIH has remained controversial so far, we still emphasize the significance of strict follow-up and close monitoring in management of such condition.

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