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# Clinical and histopathological features of asymptomatic persistent microscopic hematuria in children*

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**Background/aim:** We analyzed the clinical and pathological features and prognosis of 106 children with persistent asymptomatic microscopic hematuria (PAMH) with or without mild proteinuria.

**Materials and methods:** This was a retrospective study of 106 children who were referred to our clinics from 2000 to 2013 for evaluation of PAMH.

**Results:** Among the 106 patients, 69 (65%) were female and 37 (35%) were male. The patients were divided into two groups: 101 patients with isolated microscopic hematuria (IMH) and 5 patients with asymptomatic microscopic hematuria and mild proteinuria (AMHP). Renal biopsy was performed in all 5 children with AHMP: 2 patients had hereditary nephropathy and 2 patients had focal segmental glomerulosclerosis (FSGS). One biopsy specimen revealed nonspecific findings. Renal biopsy was performed in 9 children with IMH: 4 patients had hereditary nephropathy and 5 patients had nonspecific findings. None of the patients received any specific treatment prior to renal biopsy. During the follow-up period, none of the patients developed impaired renal function. Among all the children, only one patient with AMHP developed hypertension and 2 patients with IMH developed proteinuria.

**Conclusion:** Long-term follow-up must be done carefully for isolated microscopic hematuria and renal biopsy should be performed in selected cases.

**Key words:** Hematuria, proteinuria, renal biopsy

## 1. Introduction

Persistent asymptomatic microscopic hematuria is a common presenting symptom of renal disorders in children, with a prevalence of 1% to 2% (1). Although there is a long list of causes of asymptomatic microscopic hematuria, the vast majority of cases are benign (2). However, hematuria can be one of the most important signs of glomerular injury, especially if it becomes persistent. The American Academy of Pediatrics recommends screening urinalysis at school entry and once during adolescence (3). Despite the frequency of its detection, considerable disagreement persists about its exact nature (4).

Isolated microscopic hematuria is defined as PAMH without hypertension, proteinuria, or renal insufficiency. A questionnaire survey of North American pediatric nephrologists focused on IMH and revealed that only 5% of respondents would perform renal biopsy for this finding (5). Renal biopsy is usually recommended for patients with AMHP, while opinions about renal biopsy in children with IMH remain controversial. It is important to consider renal biopsy for early detection of asymptomatic patients, who are at risk of progressive renal disease.

In the present study, we analyzed the clinical features, pathological findings, and prognosis in 106 children with PAMH with or without mild proteinuria to assess the natural history of PAMH.

## 2. Patients and methods

This study is a retrospective study of 106 children who were referred to the Pediatric Nephrology outpatient clinics at the Marmara University Hospital from January 2000 to December 2013 for evaluation of PAMH. Microscopic hematuria with or without mild proteinuria had been detected by dipstick analysis. Microscopic hematuria was

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defined as more than 5 erythrocytes per high power field by microscopic examination of urine sediment at three consecutive visits over 4 or more weeks.

Patients with microscopic hematuria with or without mild proteinuria persisting for more than 1 year were included in the study. The patients were divided into two groups: 101 patients with IMH and 5 patients with AMHP. Two patients with IMH developed mild proteinuria during follow-up.

Patients were excluded from the study if they also had moderate-to-severe proteinuria (>0.5 g/1.73 $m^2$/24 h), renal insufficiency, hypertension, previous urolithiasis, documented macroscopic hematuria, acute or chronic glomerulonephritis (Henoch–Schönlein purpura, systemic lupus erythematosus, postinfectious glomerulonephritis), a known bleeding diathesis, or chronic systemic illness.

The diagnostic studies included serum complement concentration (C3 and C4), antinuclear antibody (ANA), urine calcium to creatinine ratio or 24-h urinary calcium excretion, urinary protein to creatinine ratio or 24-h urinary protein excretion, and renal ultrasounds. Patient records were also reviewed for family history, laboratory, and radiologic data.

An ultrasound-guided percutaneous kidney biopsy was performed in 14 cases if there was a history of PAMH persisting for at least 2 years, a positive family history of renal disease, hypocomplementemia, positivity on ANA screening test, and/or a concomitant proteinuria. We could not perform renal biopsy in 2 patients with IMH and a positive ANA test and one patient with IMH and low complement C3 level because their families did not give consent for renal biopsy. Renal biopsy specimens were examined by a renal pathologist using light microscopy, indirect immunofluorescence, and electron microscopy. Nonspecific findings in renal biopsy were defined as histopathological findings like minimal mesangial hypercellularity, expansion of the mesangial matrix, minimal thickening of the glomerular basement membrane, focal and low grade interstitial nephritis or weak immunoglobulin, and/or complement deposition in the mesangium and/or glomerular basement membrane that are not pathognomonic for any glomerular disease.

All of the 106 children were monitored through follow-up visits for 1 to 14 years. On these follow-up visits hematuria, glomerular filtration rate, proteinuria, and hypertension were examined. All data were listed in Microsoft Excel and statistical analyses were performed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).

## 3. Results

### 3.1. Demographic characteristics and laboratory findings

The results of the study are shown in Table 1. The mean age of the patients at presentation was 9 years (1–15 years). The study included 69 female and 37 male patients (female:male = 1.9:1). The median follow-up period was 6.4 years (1–14 years). Serum complement concentrations (C3) were low in three patients and two patients were positive for ANA. The frequency of hypocomplementemia and positivity on ANA screening test were not different between the groups (Table 1).

**Table 1.** Demographic and clinical characteristics of patients.

| | Biopsy (+) isolated microscopic hematuria (IMH) | Biopsy (+) asymptomatic microscopic hematuria and proteinuria (AMHP) | Biopsy (–) isolated microscopic hematuria (IMH) | Total (PAMH) |
|---|---|---|---|---|
| n (%) | 9/106 (8%) | 5/106 (5%) | 92/106 (87%) | 106 |
| Female | 8/9 (89%) | 2/5 (40%)* | 59/92 (64%) | 69 (65%) |
| Age (months) at presentation | 122 (16–168) | 131 (85–165) | 97 (13–178) | 108(13–178) |
| Follow-up (months) | 55 (16–168) | 78 (15–93) | 78 (12–150) | 77 (12–168) |
| Familial renal disease | 5/9 (55%) | 4/5 (80%)* | 30/92 (32%) | 39/106(36%) |
| Microscopic hematuria in first-degree relatives | 6/9 (66%) | 4/5 (80%) | 44/92 (47%) | 54/106 (50%) |
| Familial kidney stone | 1/9 (11%) | 1/5 (20%) | 22/92 (23%) | 24/106 (20%) |
| Low complement C3 level | 1 | 1 | 1 | 3 |
| ANA/anti-DNA positivity | 0 | 0 | 2 | 2 |

*P< 0.05

### 3.2. Family history

A positive family history of microscopic hematuria in first-degree relatives was reported in 55 (51%) patients. Nearly 22% of patients had a family history of renal stones in a first-degree relative and also 36% of them had family history of renal disease other than stone disease (Table 1). A positive family history of renal disease was significantly higher in patients with AMHP than IMH. Positive family history of microscopic hematuria was not different between the groups (Table 1). Hypercalciuria was found in only two patients and both of these patients had a family history of renal stones.

### 3.3. Histopathological findings

We performed renal biopsies in 14 (13%) patients. Of the 5 children with AMHP who underwent renal biopsy, 1 patient had Alport syndrome, 1 patient had thin basement membrane disease, 2 patients had focal segmental glomerulonephritis, and 1 patient had nonspecific findings (Table 2). Of the 9 children with IMH who underwent renal biopsy, 2 patients developed proteinuria and were diagnosed with Alport syndrome, 2 patients had thin basement membrane disease, and 5 patients had nonspecific findings (Table 2).

### 3.4. Treatment strategy

None of the patients received any specific treatment prior to renal biopsy. After renal biopsy 4 patients with AMHP received angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker (ACEi/ARB) for proteinuria and 2 patients with focal segmental glomerulonephritis received immunosuppressive treatment that included methylprednisolone and calcineurin inhibitors. None of the patients with IMH received immunosuppressive treatment. Only 2 patients with IMH who initially were nonproteinuric developed minimal proteinuria during follow-up and they were treated with ACEi and/or ARB. Both of these patients had a family history of renal diseases and were diagnosed with Alport syndrome on renal biopsy.

### 3.5. Prognosis of the patients

Among all the patients, only 1 patient with AMHP diagnosed with FSGS after renal biopsy developed hypertension, and 2 patients with IMH developed proteinuria. On the other hand, renal function tests were stable during follow-up in all of the patients.

## 4. Discussion

Persistent asymptomatic microscopic hematuria in children is one of the most common symptoms of urinary tract diseases and is usually benign and rarely a sign of a serious illness (2,6,7). However, the decision on the optimal timing of renal biopsy in children with PAMH is inconclusive.

Several studies demonstrated that patients with PAMH had a poor prognosis, particularly if there was accompanying proteinuria. Urine dipstick testing for proteinuria should be performed periodically in all patients with PAMH, because hereditary nephropathies may present with only microscopic hematuria in the early stages of the disease (2). Microalbuminuria is specific and sensitive for early detection of chronic renal disorders and renal biopsy should be performed in all pediatric patients with AMHP without question (8). In our study, positive family history of renal disease was significantly higher in patients with AMHP than IMH. Our findings suggest that a renal biopsy should be done not only in patients with proteinuria, but also in patients with a family history of renal disease.

Children with IMH have been known to have a more benign natural course than those with AMHP (9) and more attention should be paid to patients with AMHP, because their prognosis may not be optimistic. If renal biopsy is not performed until more overt signs of progressive nephropathy occur, it may cause a delay in appropriate management in the disease course. On the other hand, nonprogressive renal disorders such as thin basement membrane disease are thought to have a benign clinical course. Performing a renal biopsy in such patients

**Table 2.** Histopathological findings of the patients who underwent renal biopsy.

| | Isolated microscopic hematuria (IMH) n: 9 | Asymptomatic microscopic hematuria and proteinuria (AMHP) n: 5 |
|---|---|---|
| Nonspecific findings* | 5 (56) | 1 (20) |
| Alport disease | 2 (22) | 1 (20) |
| Thin basement membrane disease | 2 (22) | 1 (20) |
| Focal segmental glomerulosclerosis | 0 (0) | 2 (40) |

Data are presented as the number of patients, with the percentage given in parentheses

*Nonspecific findings in renal biopsy were defined as histopathological findings that are not pathognomonic for any glomerular disease.

with IMH means that a considerable number of those with benign hematuria would undergo an invasive and unnecessary procedure. Similarly, in our study, hereditary nephropathies (44%) and nonspecific findings (56%) were observed in patients with IMH who underwent renal biopsy. None of the patients with IMH received specific treatment; on the contrary, of the 5 children with AMHP who underwent renal biopsy, 2 (40%) patients had focal segmental glomerulonephritis and these patients received immunosuppressive treatment.

Several studies indicate that long-term outcomes of IMH may show an unfavorable prognosis and renal biopsy should be done at an early stage. Shen et al. reported that IMH and urinary albumin/creatinine ratio (UACR) were shown to be good markers to identify patients at high risk for glomerulopathies. They performed renal biopsy in 216 patients with IMH. All 216 patients were divided into three groups. The mean UACR in the chronic glomerulonephritis group including IgAN, mesangial proliferative glomerulonephritis, and membranous glomerulonephritis was higher compared with that in the TBMN or normal group (10). Cho et al. performed renal biopsies in 997 (26.7%) of a total of 3724 children with IMH in a nationwide study and reported that the incidence of glomerulonephritis was 22.88% in the isolated hematuria group and the rate of no pathologic abnormality on renal biopsy was about 15%. Therefore, the authors pointed out that the definitive indication of renal biopsy for IMH remains unclear (11). Lee et al. also analyzed 461 cases of renal biopsy performed in children with abnormal results in school urinary mass screening tests. Among these children, 289 patients (62.7%) had IMH and there was a relatively high rate of pathological abnormalities on renal biopsy in the group with microscopic hematuria combined with proteinuria (12). Lin et al. analyzed 573 school children in Taiwan, and they showed that 46.4% of the children had persistent IMH and 14.3% of the children had AHMP and demonstrated that children who had IMH are at the same risk for important glomerulopathies as well as children who had coexisting proteinuria. In the present study, IgAN, SLE, and benign hematuria were the majority of underlying diseases in the IMH group. We did not show any IgA nephropathy in any case of renal biopsy performed in children in contrast to other studies, because we excluded patients with at least one macroscopic hematuria attack from our study group. They showed that even in patients with class 3–4 lupus nephropathy might present with only microscopic hematuria (13). Vivante et al. reported that the presence of IMH was associated with significantly increased risk of ESRD for a period of 22 years, a quite long and valuable follow-up time. In that study IMH was diagnosed in 3690 of 1,203,626 individuals who were 16 through 25 years of age. During 22 years of follow-up, ESRD developed in 26 (0.7%) individuals with IMH and 539 (0.045%) with other causes like diabetes, hypertension, hereditary nephritis, interstitial nephritis, and cystic kidney diseases (14). We also closely followed-up for up to 15 years the children in which we had not performed biopsy. In our study, none of the patients with IMH developed hypertension or impaired renal function during follow-up and with that long period of follow-up time, our findings are favorable in terms of not performing early biopsy during the course of IMH in our age group. If we had performed renal biopsy in all of our patients, we could also have found more pathological abnormalities.

Our results suggest that the prognosis of patients with IMH may be favorable and, in cases of asymptomatic patients with IMH, renal biopsy can be postponed due to its favorable nature. For children accidentally found to have IMH, the decision whether to perform a renal biopsy remains questionable. On the other hand, evaluation for the necessity of renal biopsy is essential. Therefore, a renal biopsy may be optional for patients with IMH, and screening for the presence of proteinuria is a useful tool for performing renal biopsy in patients with PAMH.

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