
Asymptomatic isolated microscopic haematuria: long-term follow-up

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Summary

Background: Evidence to support current diagnostic and management approaches to asymptomatic haematuria is lacking and based on short-term clinical observation.

Aim: To ascertain the natural history and long-term outcome of asymptomatic and isolated haematuria, and to determine the clinical correlates of adverse renal events.

Design: Prospective observational referral-based study.

Methods: We evaluated 90 consecutive patients with isolated microscopic haematuria, first seen between 1985 and 1996 at an out-patient nephrology clinic. We defined adverse renal events as the development of proteinuria (>0.5 g/24 h) on two consecutive occasions, development of hypertension, or impaired renal function characterized by glomerular filtration rate (GFR) of <60 ml/min/ 1.73 m² for 3 months or more.

Results: There were 24 males and 66 females, median follow-up 5.2 years (total 442 patient-years). Mean age at presentation was 39 ± 13 years. Fifteen (17%) had complete resolution of

microscopic haematuria. One (1%) had transitional cell carcinoma of urinary bladder 20 months after initial presentation. Twelve (13%) developed hypertension, and 10 (11%) proteinuria. Only one developed chronic renal failure, 2.3 years after initial presentation. Altogether, 16 (19%) developed at least one adverse event, after a mean 42 months. Neither history of renal biopsy nor histological diagnosis of glomerular disease was predictive of renal events. Three independent variables were predictive of adverse renal events: baseline proteinuria (RR per 0.1 g/day 2.04; 95%CI 1.13–3.68; $p=0.018$); MDRD-estimated GFR at presentation (RR per 10 ml/min/ 1.73 m² decrement 2.01; 95%CI 1.09–3.71; $p=0.025$); and baseline serum urate (RR per 100 μ mol/l 1.02; 95%CI 1.01–1.03; $p=0.009$).

Discussion: Asymptomatic microscopic haematuria can lead to adverse renal events, and warrants nephrologist evaluation and regular follow-up. Its isolated microscopic haematuria is closely related to early hints of chronic kidney disease, such as low-grade proteinuria and renal insufficiency, as well as hyperuricaemia.

Introduction

Studies to support current recommendations regarding the evaluation and management of isolated asymptomatic haematuria are long overdue,^{1–3} even though this condition is frequently encountered in clinical practice. There is controversy regarding

which tests are routinely indicated,^{1,4,5} and the yield of testing and its effect on outcomes are uncertain. It is also controversial whether renal biopsy is indicated for isolated microscopic haematuria alone.⁶ Most important of all, the natural history

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and risk of microscopic haematuria need to be evaluated by prolonged follow-up of all patients after initial presentation.

Our aim was to assess the long-term outcome for asymptomatic and isolated haematuria. By 'isolated haematuria', we mean the presence of erythrocytes in the urine in abnormal quantities (two or more red cells per high-power field on microscopical examination) without any other abnormalities in the urine.^{1,7-9} It is important to address the key clinical questions relating to asymptomatic isolated microscopic haematuria alone, because most previous series were either short-term retrospective referral-based or heterogeneous studies including other symptoms such as macroscopic haematuria and/or with proteinuria.

Methods

Study participants

We included patients who were older than age 15 years and being evaluated in the ambulatory out-patient nephrology facility at the Prince of Wales Hospital. All persons seen between 1985 and 1996 were screened for eligibility, and 90 consecutive individuals with isolated microscopic haematuria were enrolled. Patients with baseline proteinuria in excess of 0.5 g/24 h were excluded. According to the American Urological Association Best Practice Policy Recommendation, microscopic haematuria in the presence of significant proteinuria, defined as >0.5 g/24 h, warrants evaluation and nephrology referral.^{10,11}

Evaluation consisted of history and examination, urinalysis and cytology, blood tests, and if indicated, cystoscopy and imaging. Urinary abnormality was detected semi-quantitatively by orthotolidine-impregnated paper strips (Hemastix, Bayer Diagnostics Manufacturing) and confirmed by microscopic evaluation of properly collected urinalysis specimens. Estimation of the degree of haematuria was further performed by counting the number of erythrocytes present per high-power field (phpf) when the resuspended sediment obtained by light centrifugation (relative centrifugal force of 400 g for 5 min according to the National Committee for Clinical Laboratory Standards NCCLS¹²) of a freshly voided urine specimen was examined under contrast microscopy with high-power magnification (400 \times).⁸ Dysmorphic urinary red cells were indicated by acanthocytes with characteristic ring-formed erythrocytes and vesicle-shaped protrusions.¹³ Urinary protein was tested by reagent strips (Albustix, Bayer Diagnostics Manufacturing)

and, in the absence of urinary tract infection, quantified by 24 h urinary collection.

Cytological analysis of urine specimens from the first voiding in the morning on three consecutive days were obtained from all subjects to complete the evaluation of the lower urinary tract; renal ultrasonography and cystoscopy were reserved for cases without identified cause of microscopic haematuria. Intravenous excretory urography imaging was performed in high-risk patients.

We entered details of participants into a computerized database at the time of their first clinic visit. We further added information including demographic data (gender, body mass), clinical details (symptomatology, blood pressure), renal function (concentrations of urea and creatinine), biochemistry panel and serological studies (antinuclear body, antineutrophil cytoplasmic antibodies by indirect immunofluorescence testing, immunoglobulin levels, serum protein electrophoresis and viral hepatitis markers), self-reported and physician-reported data at follow-up visits. Estimated glomerular filtration rates were retrospectively evaluated by the Cockcroft-Gault equation¹⁴ and the Modification of Diet in Renal Disease MDRD Study equation.^{15,16} Systematic longitudinal comorbidity and renal outcomes was ascertained.

Definition of adverse renal events

Adverse renal events included development of proteinuria (>0.5 g/24 h) on two consecutive occasions, development of hypertension (systolic blood pressure \geq 140 mmHg and/or diastolic blood pressure \geq 90 mmHg)¹⁷ and need for antihypertensive therapy, and impaired renal function or chronic renal failure, as defined by glomerular filtration rate of <60 ml/min/1.73 m² (representing loss of more than half the normal young-adult level of kidney function)¹⁶ for 3 months or more.

Statistical analysis

Analyses used Statistical Package for the Social Sciences software for Windows, version 11.0 (SPSS). Data are expressed as means \pm SD unless otherwise specified. Data were compared by Student's *t*-test, the χ^2 test, or Fisher's exact test, as appropriate. Univariate analysis was used to explore the association between clinical factors and development of composite adverse renal events. Kaplan-Meier method with log-rank tests was used to compare the incidences of adverse renal events.¹⁸ Cox proportional hazard models were built to examine independent predictors of adverse renal events, as constructed from variables encompassing covariates identified by our investigation and previous studies.

Variables included age at presentation, body weight, mean arterial pressure, degree of initial proteinuria, MDRD equation estimated glomerular filtration rate at presentation and serum urate concentration. Backward stepwise elimination was used to remove insignificant ($p > 0.05$) variables. p values are two-sided.

Results

A series of 90 consecutive Chinese patients was identified in our nephrology clinic with a diagnosis of isolated microscopic haematuria and median follow-up period of 5.2 years (a total of 442 patient-years of follow-up). There were almost three times as many females (66) as males (24) in the cohort. Mean age at presentation was 39 ± 13 years (range 15–77). Less than one-fifth (16%) of patients had family history of renal disease.

Examinations of their urinary sediment detected a median of 4 red cells per high-power field, with range from 2–30 red cells phpf. Dysmorphic red cells were encountered in 35 (39%) of the whole group of patients with microscopic haematuria. At the entry to the study, total urinary protein excretion measured 0.2 ± 0.1 g/24 h. By Cockcroft-Gault equation estimation, the baseline creatinine clearance measured 99.5 ± 30.0 ml/min,

corresponding to serum creatinine concentration of 71.6 ± 16.9 μ mol/l. Estimated glomerular filtration rate was 96.9 ± 24.1 ml/min/1.73 m², according to the abbreviated MDRD Study equation. Only nine of the patients (10%) had baseline blood pressure exceeding 140/90 mmHg; overall, the cohort's mean arterial pressure was 90 ± 12 mmHg. Mean serum urate concentration was 293 ± 81 μ mol/l.

Hepatitis B surface antigen was found in eight patients (9%), in keeping with the local prevalence of hepatitis B disease.¹⁹ Seven patients had anti-nuclear antibody titre in excess of 160—none of them had positive antineutrophil cytoplasmic antibodies. Their serum immunoglobulin A (IgA) levels were 3.2 ± 1.1 g/l (normal range 0.8–4.0 g/l) and were elevated in 31% of the cases.

Figure 1 shows a flow diagram of the study population. Fifteen patients (17%) had complete resolution of microscopic haematuria, after a median follow-up interval of 1.4 years. Out of the 32 patients who underwent intravenous excretory urography, a possible cause of haematuria was demonstrated in one patient. Among them, one patient developed serious urological disease (urinary bladder transitional cell carcinoma) after 20 months.

Of the 28 patients (31%) who underwent renal biopsy, eight patients had histological and

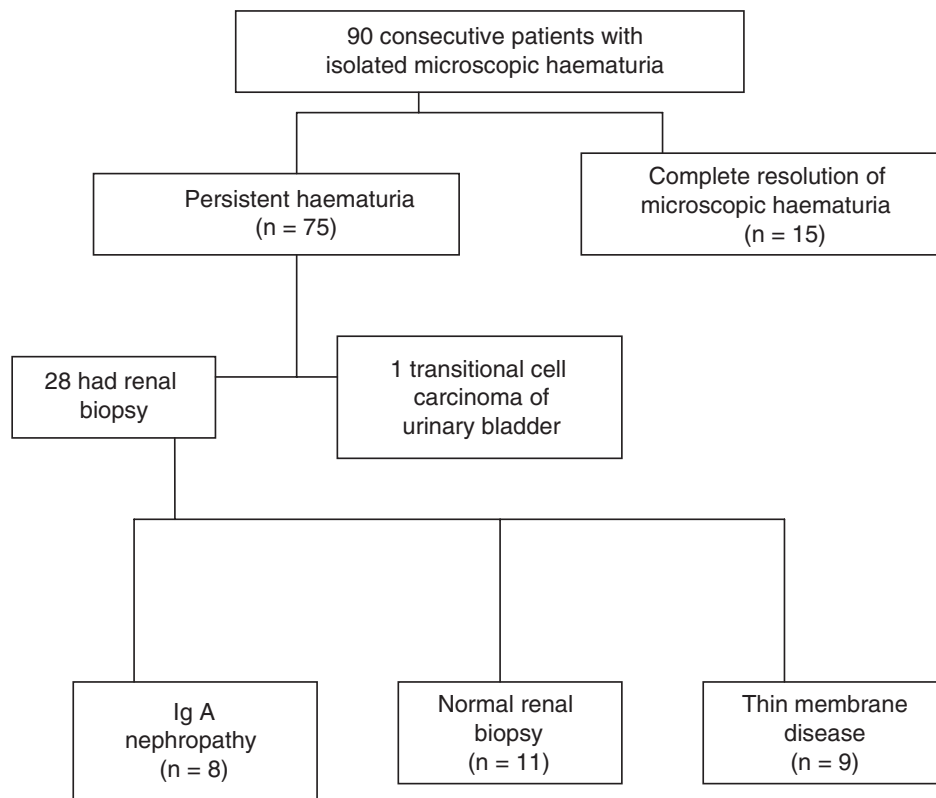


Figure 1. Flow chart of study participants.

immunofluorescence evidence of IgA nephropathy. Normal renal tissue was found in 11 patients. Thin glomerular basement membrane was noted in nine patients who were biopsied, five of whom had documented high-tone hearing loss by audiometry. Overall, high-tone hearing loss was documented in 10/22 patients who underwent pure tone audiometry.

During the follow-up period, 12 patients (13%) developed hypertension. Ten patients (11%) developed proteinuria exceeding 0.5 g daily. At the end of follow-up, the average 24-h urinary protein was 0.2 g daily, and glomerular filtration rate was 75.2 ± 19.1 ml/min/1.73 m². As defined by glomerular filtration rate of <60 ml/min/1.73 m² for 3 months or more, chronic renal failure occurred in only one patient (1%) at 2.3 years after initial presentation. Altogether, 16 patients (19%) developed at least one adverse event, with a mean interval of 42 months for the progression to the composite end-point of adverse renal events.

Patients who developed adverse renal events had a greater degree of proteinuria, and somewhat higher mean arterial pressure, serum urate level and body weight at initial presentation (Table 1) according to univariate analysis, without taking into account the time to event. The cumulative probability of developing an adverse renal events at 2 years was 18.5% for those with baseline proteinuria >0.1 g/day (Figure 2), compared with

3.2% for those with proteinuria ≤ 0.1 g/day ($p=0.016$). There was no statistically significant difference in event rate with respect to patient smoking habit. The degree of microscopic haema-

Table 1 Clinical characteristics at the time of presentation, by the subsequent development of adverse renal events

	Developed adverse renal events (n=16)	No adverse events (n=74)	p
Age (years)	40 ± 12	39 ± 13	0.82
Female	11 (69%)	55 (74%)	0.76
Body weight (kg)	62.2 ± 13.0	56.8 ± 9.8	0.06
Mean arterial pressure (mmHg)	94 ± 13	89 ± 12	0.11
Systolic blood pressure (mmHg)	130 ± 18	124 ± 17	0.97
Baseline proteinuria (g/day)	0.3 ± 0.1	0.2 ± 0.1	0.02
Baseline GFR by MDRD estimation ¹⁶ (ml/min/1.73 m ²)	99 ± 24	96 ± 24	0.67
Serum urate concentration (µmol/l)	340 ± 90	280 ± 80	0.07
Positive family history of renal disease	5 (32%)	9 (12%)	0.12

GFR, glomerular filtration rate.

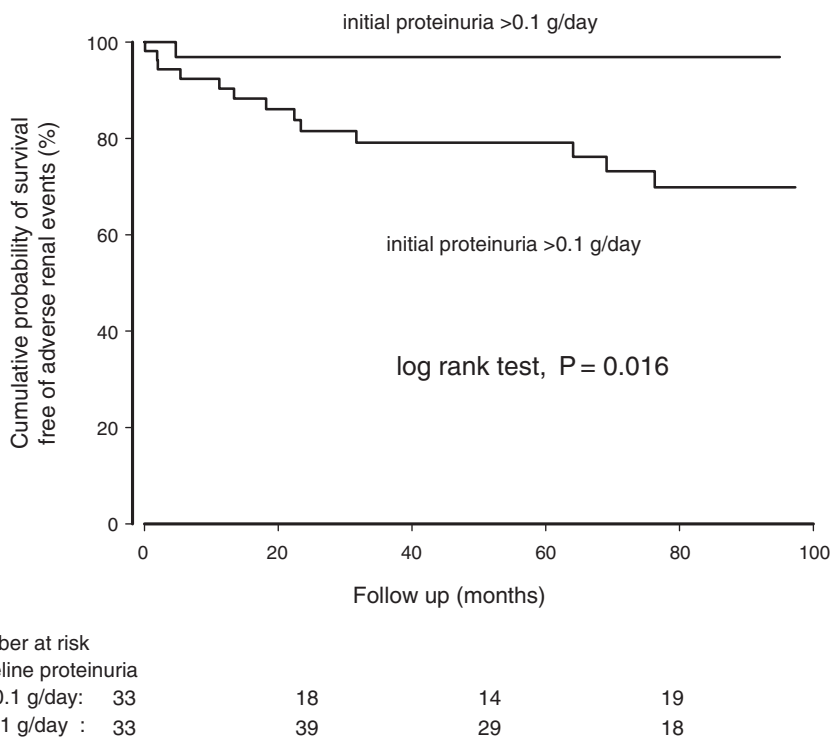


Figure 2. Cumulative probabilities of adverse event-free survival.

turia and morphology of urinary red blood cells did not differentiate between those with and without adverse renal events. The mean event-free survival rate (for the composite end point of adverse renal events) was similar with reference to renal biopsy history (152 months in the group who were biopsied and 118 months among those not undergoing renal biopsy, $p=0.92$). Of the 17 patients with a histological diagnosis of glomerular disease (IgA nephropathy and thin membrane disease), the mean event-free survival rate was 115 ± 21 months, similar to the rate of 177 ± 11 months in the group of patients with no pathology confirmed or without renal biopsy ($p=0.15$ by the log-rank test).

Finally, in a multivariate model (Cox proportional hazards), three factors were independently associated with increased risk of adverse renal events. Baseline proteinuria (relative risk per 0.1 g/day = 2.04; 95%CI 1.13–3.68; $p=0.018$) and MDRD estimated glomerular filtration rate at presentation (relative risk per 10 ml/min/1.73 m² decrement = 2.01; 95%CI 1.09–3.71; $p=0.025$) were associated with adverse renal events, as was patient baseline serum urate level (relative risk per 100 $\mu\text{mol/l}$ = 1.02; 95%CI 1.01–1.03; $p=0.009$).

Discussion

With a median follow-up period of 5.2 years, our study provided a unique opportunity to examine the long-term outcome and natural history of isolated microscopic haematuria. The strengths of this study include the uniform case ascertainment and prospective long-term follow-up. Although it was not large enough to establish practice guidelines for microscopic haematuria, it adds to the growing body of evidence that asymptomatic isolated microscopic haematuria might not appear as benign as we might have thought previously.^{20,21} The present study raised the concern about potentially progressive renal disease or hypertension that may present with asymptomatic microscopic haematuria, even in the absence of significant proteinuria or hypertension initially.^{22–24} By the end of 2 years, more than one-fifth (22%) of the patients with isolated microscopic haematuria developed adverse renal events, as defined *a priori* by the composite end point of new onset proteinuria, hypertension or chronic renal failure according to our series.

Our data did not suggest a difference in term of renal prognosis among patients with biopsy-proven glomerular disease presenting with isolated microscopic haematuria vs. those without undergoing renal biopsy. It has been demonstrated that renal

biopsy performed on the basis of haematuria alone would not change the therapy.²⁵ The possible clinical implications to be drawn from our study appears to be that renal biopsy confirmation of pathological diagnosis of isolated microscopic haematuria is of minimal prognostic importance.

Given the remarkable heterogeneity of cases with isolated microscopic haematuria, it would be astonishing—and challenging—if common prognostic factors were to be identified. In this regard, our results deserve attention, in that they confirm independent risk factors common to a representative, albeit diverse, population with the diagnosis of isolated microscopic haematuria and minimal proteinuria.

A few comments are in order relating to the limitations of our study design. Clearly, there is legitimate concern that results from this referral-based study might not be comparable with those from community-based studies. Notwithstanding the possible bias from our cohort recruitment, our data closely resemble results from large-scale epidemiological population-based studies. For instance, in a study 432 adults with asymptomatic microscopic haematuria diagnosed in the mass screening programme,²⁶ with a similar mean follow-up period to ours, 10.6% developed proteinuria, as compared to 11% reported in our study.

From the nephrologist perspective, the presence of red cells in the urine, even in the context of minimal proteinuria, should prompt the course of action that heightens awareness of early asymptomatic kidney disease. As borne out by our analysis, detailed evaluation of the renal function was warranted; each 10 ml/min/1.73 m² glomerular filtration rate reduction or each 0.1 g/day proteinuria at baseline was noted to confer a two-fold relative risk of developing adverse renal events.

Furthermore, the serum urate level was found to be an independent risk factor for adverse renal outcomes among patients with isolated microscopic haematuria. This observation is in accordance with another two studies which have established that hyperuricaemia is an independent risk factor for progression in IgA nephropathy.^{27,28} Moreover, in a recent study of 6400 subjects with normal baseline renal function, a serum urate concentration >480 $\mu\text{mol/l}$, as compared with a serum urate level <300 $\mu\text{mol/l}$, was associated with a 2.9-fold increased risk for developing renal insufficiency within 2 years in men and 10.0-fold increased risk in women.²⁹ In another large study of 49 413 male subjects, a serum urate level >510 $\mu\text{mol/l}$ was associated with a 8.5-fold increased risk of renal failure.³⁰ Clearly, further studies are needed to determine whether early

treatment of hyperuricaemia can improve the prognosis of isolated microscopic haematuria or progressive renal disease.

In summary, the degree of proteinuria, baseline glomerular filtration rate and hyperuricaemia constitute independent and important mediators of renal progression among a group of patients of isolated asymptomatic microscopic haematuria. All these factors might provide early hints of chronic kidney disease, and most important of all, are closely related to the prognostic significance of isolated microscopic haematuria. Attention should be paid to these previously underestimated risk factors even in a subgroup of patients with so-called minor glomerular diseases or non-proteinuric haematuria. It is worth considering isolated microscopic haematuria as Stage 0 according to the current National Kidney Foundation staging of chronic kidney disease,¹⁶ indicative of patients at risk of developing chronic kidney disease.

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