Glomerular haematuria: not so benign?

H.P.E. Peters*, L.B. Hilbrands, J.F.M. Wetzels

Department of Nephrology 464, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, *corresponding author: tel.: +31 (0)24-361 47 61, fax: +31 (0)24-354 00 22, e-mail: h.peters@aig.umcn.nl

INTRODUCTION

Isolated haematuria is a frequent finding in routine clinical practice. In most cases haematuria is caused by glomerular disorders, in particular IgA nephropathy (23 to 75%), thin basement membrane nephropathy (5 to 35%), and non-IgA mesangiproliferative glomerulonephritis (9 to 24%). Prognosis is considered to be good in these patients provided proteinuria, hypertension, and renal insufficiency are absent. Hence the term benign glomerular haematuria has been used to describe this condition. In many parts of Europe and the USA a renal biopsy is considered unnecessary in these patients, and they are referred to their general physician for life-long (bi)annual monitoring of serum creatinine concentration, proteinuria and blood pressure.

In this issue of the Netherlands Journal of Medicine, Shen et al. present their analysis of patients with clinically early IgA nephropathy, defined as biopsy-proven IgA nephropathy with haematuria and no or minimal proteinuria, normal blood pressure, and normal renal function. The authors show that after a mean follow-up of ten years progressive renal failure occurred in up to 24% of patients.

What lessons can be learned from these data and should we adopt a more vigorous renal biopsy policy?

HAEMATURIA IS A COMMON PROBLEM

In China and other Asian countries screening programmes are used to identify persons with minimal urinary abnormalities. Shen et al. report a prevalence of haematuria in the screened population of 8.5%. Similar prevalence rates have been reported for the European population, with a range of 0.8 to 16.1%. This wide range results from the variance in age and sex distribution of the populations studied and whether the diagnosis was based on dipstick test alone or also on microscopic examination of the urinary sediment.

IMPORTANT TO DIFFERENTIATE BETWEEN GLOMERULAR AND NONGLOMERULAR HAEMATURIA

Although microscopic haematuria is generally of glomerular origin, it is important to exclude urological causes. The latter is even more important in the elderly, where haematuria more often results from malignancies such as bladder carcinoma. Shen et al. performed urological investigations in all patients with haematuria to exclude urological causes. Of note, the authors do not mention the urinary sediment as an important tool to differentiate between glomerular and nonglomerular haematuria. Glomerular haematuria is characterised by the presence of dysmorphic erythrocytes, whereas in urological diseases monomorphic erythrocytes are observed. Moreover, the presence of erythrocyte casts is virtually pathognomonic for glomerular haematuria.

In a study designed to evaluate the significance of dysmorphic erythrocytes in the urinary sediment for discrimination between urological and nephrological causes of haematuria, the percentage of dysmorphic erythrocytes was determined in urine samples of 107 patients with known glomerular or urological haematuria. When different thresholds for the number of dysmorphic erythrocytes were chosen, a percentage of dysmorphic erythrocytes of 40% or less had a sensitivity of 100% and a specificity of 67% to diagnose urological haematuria. In other words when using this threshold no urological causes of haematuria would be missed, although 33% of patients with glomerular haematuria would falsely be presumed to suffer from an urological disease and might therefore unnecessarily be subjected to urological investigations. When the presence of erythrocyte casts was also considered a criterion for nephrological pathology, the specificity to diagnose urological pathology rose to 88.1% while sensitivity remained 100%. Importantly, when urinary sediment is not performed as initial diagnostic procedure in the evaluation of haematuria, the number of patients who are unnecessarily exposed to urological examinations will be much higher.
Thus, a thorough investigation of the urinary sediment by an experienced technician or physician according to strict criteria is a reliable aid in determining the optimal strategy to be followed in patients with haematuria. Adopting an approach for the evaluation of haematuria which includes initial screening of the urinary sediment prevents many unnecessary, expensive and often invasive urological tests. In the study by Shen et al., most patients with progression (91%) developed proteinuria >1 g/day. Of note, this level of proteinuria was also the threshold for progression in a recent study by Reich et al.14 These authors reported the clinical course in 542 patients with IgA nephropathy. Patients received variable treatment regimens. It appeared that if proteinuria was lowered to values below 1 g/day no progression occurred.

**Proteinuria, Not Haematuria, Determines Renal Outcome**

Shen et al. observed that 24% of patients developed renal insufficiency (defined as estimated GFR <60 ml/min/1.73 m^2) during follow-up. Similar results were reported by Szeto et al. who studied a cohort of 72 patients with IgA nephropathy, haematuria and minimal proteinuria.15 After a median follow-up period of seven years, more than 40% of the patients had evidence of progressive renal injury as determined by proteinuria (33%), hypertension (26%) or impaired renal function (7%). Other studies have also shown that haematuria is an independent risk factor for the development of chronic kidney disease.11 Taken together, these data suggest that patients with glomerular haematuria have a less favourable prognosis. Thus, haematuria might not be so benign after all.

When the data are scrutinised in more detail, it appears that patients with persistently isolated haematuria do not develop renal insufficiency. In fact, it is proteinuria that counts. In the study by Shen et al. progressive renal failure only occurred in patients who had proteinuria at baseline or developed proteinuria during follow-up. Similar observations were made by other investigators studying the prognosis of patients with asymptomatic haematuria.12-4,5,10 In these studies, approximately 10% of the patients developed proteinuria during the follow-up period. While 10 to 15% of the patients with proteinuria subsequently developed renal insufficiency, none of the patients with persistent isolated haematuria exhibited a decline of renal function. Thus, impairment of renal function only occurred in patients who had developed proteinuria and often also hypertension. Consequently, a renal biopsy will not aid in the management of patients with haematuria with no or only slight proteinuria. Current practice consisting of life-long follow-up with monitoring of blood pressure and proteinuria at regular intervals will allow timely identification of those patients with haematuria at risk for progression to renal insufficiency. Postponing a renal biopsy until proteinuria becomes evident is therefore justified, particularly since renal biopsy is an invasive procedure with a small but significant risk of complications.

**Prednisone Treatment May Be Effective**

Reduction of proteinuria is the mainstay of treatment in patients with IgA nephropathy. It is evident that the natural history of IgA nephropathy can indeed be modified by therapeutic interventions with either ACE inhibitors,13-14 angiotensin II-receptor blockers (ARBs),15 or the combination of these drugs.16 Kobayashi et al. have pointed to the benefits of steroid therapy in patients with IgA nephropathy.17,18 The best rationale for corticosteroids in patients with IgA is derived from a randomised controlled trial in patients with a glomerular filtration rate greater than 70 ml/min and proteinuria between 1 to 3.5 g/day.19,20 Patients were assigned randomly to supportive therapy only or additional corticosteroids. After ten-year follow-up, serum creatinine levels had doubled in one of 43 patients in the steroid group vs 13 of 43 in the control group (p<0.01). After one year, in 11 (26%) of the treated patients proteinuria had decreased below 0.5 g/day. Whether these results can be generalised has been questioned since in the study by Pozzi et al. only six patients in each group were treated with ACE inhibitors. Shen et al. add some useful information. They treated all patients with proteinuria with ACE inhibitors and/or ARBs. If despite this treatment proteinuria exceeded the level of 1 g/day additional prednisone therapy was advised. Overall, 52 of 177 patients received prednisone. The majority of patients responded to prednisone and no less than 66% of the prednisone-treated patients achieved a complete remission defined as proteinuria below 0.15 g/day. Thus, also in patients on ACE inhibitor treatment prednisone may be effective.

**Conclusion**

IgA nephropathy is a common cause of isolated microscopic haematuria. The classical course of patients with IgA nephropathy and isolated haematuria is quite variable, and up to 20% of patients will progress to ESRD in 20 years.21 A policy of biopsying all such patients is not without risk and does not influence therapy. All patients need to be carefully followed for the development of proteinuria and/
or hypertension as signs of future progression. Obviously, many patients will be followed unnecessarily. Ideally, in the near future, it should be possible to identify those patients who are at risk for progression with a noninvasive test using more sophisticated biomarkers.

REFERENCES