Current nephrological practice in the investigation of haematuria: relationship to incidence of IgA nephropathy

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Patients found to have microscopic haematuria are frequently referred for urological assessment, which will include renal imaging and cystourethroscopy. Although urological practice in the investigation of haematuria is well defined and algorithms have been presented [1, 2], a nephrological consensus, particularly with regard to the role of renal biopsy in those patients in whom a urological cause for haematuria is not found, has not been defined.

It is clear, however, that renal biopsy will uncover significant glomerular disease even when microscopic haematuria is the only abnormality found on clinical and biochemical screening and urine microscopy. Diagnoses encountered will include Alport’s syndrome and thin membrane nephropathy [3], but numerically the most important may be IgA nephropathy which, despite its apparently innocuous presentation in many cases, is a diagnosis of great importance since natural history studies increasingly show that many patients with IgA nephropathy will eventually develop chronic renal failure [4].

IgA nephropathy was once thought to be less common in the UK and the USA than in other countries [5]. In Japan and France the incidence is 40% and 30% of all biopsies performed for primary glomerular disease, in contrast with 4% found in an early study in the United Kingdom [6], with 10% recorded by the MRC Glomerulonephritis Registry [7] and with an incidence of less than 10% in a number of studies from North America [5]. However, two recent studies from the United Kingdom suggest an incidence of IgA nephropathy of more than 20% [8, 9].

Many patients with IgA nephropathy present with persistent microscopic haematuria, and it is this group of patients in particular in whom this diagnosis has been made more frequently in one recent UK study [9]. This suggests that a major factor influencing the apparent incidence of IgA nephropathy may be the attitude of individual clinicians to the use of biopsy in patients with microscopic haematuria.

This study was designed to elucidate the current nephrological practice in the UK in this field and to seek evidence that the apparent incidence of IgA nephropathy in this country may, at least in part, reflect variations in attitudes to renal biopsy.

Methods

A questionnaire was sent to all consultants and senior registrars practising adult and paediatric nephrology in the United Kingdom. Attitudes assessed by the questionnaire were:

1. Need for renal biopsy in different age groups with asymptomatic microscopic haematuria, whether isolated or in combination with proteinuria or with intermittent episodes of macroscopic haematuria. This question was confined to patients with preserved renal function and normal renal imaging.
2. Use of renal biopsy to diagnose glomerular disease in contracted kidneys.
3. Use of in vitro methods (such as phase contrast microscopy and Coulter analysis) for distinguishing glomerular from non-glomerular haematuria.
4. Other factors influencing the decision to perform renal biopsy.

Additional information sought was:

5. Pattern of referral of patients with microscopic haematuria to nephrologists.
6. Incidence of IgA nephropathy among patients with biopsy-proven glomerular disease.

Results

Distribution of responses

The questionnaire was sent to 191 doctors (163 adult and 28 paediatric nephrologists). Replies were received from 135 (70.6%), representing opinion in 89.5% of 76 nephrology centres (60 adult, 16 paediatric) in the UK. The response rate was 75% among

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senior registrars and 64.5% among consultant and professorial staff. Response was higher among paediatric nephrologists (75%) than among adult nephrologists (69.9%). Of the 163 adult nephrologists 58 (36%) indicated sufficient paediatric practice to reply to questions relating to the investigation of children.

1. Indications for renal biopsy in haematuria

Assuming that serum creatinine concentration, contrast urography and cystoscopy were normal, would you perform a renal biopsy in the following categories of patients?

The categories of patients defined and the results are presented in Table 1. The coexistence of proteinuria with haematuria was almost universally regarded as an indication for renal biopsy. However, in the absence of proteinuria, biopsy was less frequently performed in those with microscopic haematuria (with or without episodic macroscopic blood). In all categories biopsy was used more liberally in adults aged 15–65 years than in children or the elderly. There were no major differences in the range of attitudes to renal biopsy in children between paediatric nephrologists and adult nephrologists with some paediatric practice.

A ‘biopsy score’ was empirically allocated to allow comparison of individual practice: scoring 2 for ‘yes’, 1 for ‘sometimes’, 0 for ‘never’, expressed as a function of the number of patient categories to which the nephrologist responded. Thus a score of 2.0 indicated that all patients with haematuria would have a biopsy, and 0 that no biopsies were performed. Median and range of biopsy score did not differ between adult and paediatric nephrologists (1.40 ± 0.40 vs 1.34 ± 0.50), or between senior registrars and consultants/professors (1.47 ± 0.34 vs 1.29 ± 0.46).

2. Renal biopsy in patients presenting late with contracted kidneys

Renal biopsy to clarify a presumptive diagnosis of chronic glomerulonephritis in patients presenting late with contracted kidneys and urinary abnormalities was not widely used in adult (6% yes; 41% sometimes; 52% no) or paediatric (5% yes; 36% sometimes; 59% no) practice.

3. Laboratory assessment of haematuria: glomerular or non-glomerular?

Phase contrast microscopy was used by 44% of responders, and only 63% of them felt it was diagnostically helpful. Coulter counter analysis was less frequently used—by only 10% of responders, of whom only 67% were convinced of its value. For the laboratory assessment of urine 46% used only conventional microscopy for cells and casts.

4. Other factors influencing the decision to recommend renal biopsy

The presence of deafness (79%) or a family history of renal disease (77%) were both widely regarded as positive indications for biopsy.

Responders were offered the opportunity on the questionnaire to cite additional specific factors which modified their view of the need for renal biopsy. The following views were most frequently stated:

- Identification of casts on urine microscopy
- Need for a definite diagnosis, eg work/immigration/armed forces/insurance requirements

Table 1. Use of renal biopsy in the investigation of haematuria.

| Number of nephrologists responding | Children (age <15 years) | Age 15–65 years | Age >65 years |
|-----------------------------------|--------------------------|----------------|--------------|
|                                   | 12 paediatric nephrologists | 58 adult nephrologists | 106 | 106 |
| Persistent microscopic haematuria; no proteinuria | Yes: 20% (50%) No: 30% | Yes: 20% (40%) No: 40% | Yes: 36% (46%) No: 18% | Yes: 10% (53%) No: 37% |
| Microscopic haematuria + episodic macroscopic haematuria; no proteinuria | Yes: 40% (50%) No: 10% | Yes: 50% (40%) No: 10% | Yes: 69% (26%) No: 5% | Yes: 32% (58%) No: 10% |
| Microscopic haematuria + proteinuria | Yes: 85% (15%) No: — | Yes: 77% (19%) No: 4% | Yes: 89% (11%) No: — | Yes: 61% (34%) No: 5% |

Yes = biopsy always indicated. No = biopsy never indicated. Those responding that biopsy was ‘sometimes’ indicated are given in parentheses.
— Need to reassure patient, parents or referring doctor
— Need to prevent repeated urological investigation for ‘unexplained’ haematuria
— Need to clarify the prognosis in young women planning pregnancy
— Need for genetic counselling in putative inherited disease
— Need for accurate diagnosis so that the natural history of glomerular disease can continue to be defined more fully
— Persistence of microscopic haematuria over a period of observation (this view was particularly stated by paediatricians although there was no tight consensus over the duration of observation justified before biopsy; periods of 6–12 months were proposed)

Against biopsy:
— Intermittent haematuria
— Improbability that biopsy findings would modify immediate clinical management
— Good prognosis of IgA nephropathy in childhood would justify a delay in diagnostic biopsy until adulthood (Paediatricians)
— Concern that IVU and cystoscopy were not adequate screening tests for malignancy in older patients with haematuria; further imaging, particularly CT scanning, should be considered before biopsy is undertaken

5. Source of referral of patients with haematuria to nephrologists

In paediatric practice referral was most frequently from general paediatricians (47.5%) and general practitioners (40%), the remainder from urologists (12.5%). In adult practice referral from a urologist was more common (34%) and from other hospital specialists less frequent (14%), the remaining cases (52%) coming from general practitioners and other sources of routine medical examinations (e.g. life insurance, employment assessment).

6. Incidence of IgA nephropathy

Nephrologists were asked to provide an estimate of the incidence of IgA nephropathy in their population, expressed as a percentage of all biopsies performed for primary glomerular disease. Incidences in the 50 units who provided data varied widely from 5% to 70% (median 16%).

The estimated incidence of IgA nephropathy in the 50 units was assessed in the light of the average biopsy score for the nephrologists in that unit derived from the questionnaire responses. There was a significant correlation ($\rho = 0.03$) between estimated incidence of IgA nephropathy and biopsy score.

Unique data were available from two units where a single histopathologist had successively provided the sole renal histopathological opinion. An apparently low incidence of IgA nephropathy in one unit (5%) equated with a low biopsy score (0.5) for the one nephrologist there. By contrast, a high incidence of IgA nephropathy (25%) was paralleled by a high biopsy score (mean 1.83) in the other unit.

Discussion

Asymptomatic microscopic haematuria has an incidence in adults of 1–2.5% [10–13]. These patients are most commonly referred for urological assessment, a practice justified by the high incidence of major urological abnormality, up to 20% in patients over 40 years of age, in half of whom the lesion will be malignant [14, 15]. When contrast urography and cystoscopy are normal it is usually held in urological reports that renal biopsy is unnecessary unless proteinuria, urinary casts or hypertension point to a diagnosis of glomerular disease of poor prognosis [16]. However, clinical nephrological practice suggests that such an approach is falsely reassuring [17], and it is increasingly clear that glomerulonephritis, most commonly IgA nephropathy, may present with microscopic haematuria as the only abnormality (casts being absent even on repeated urine microscopy) but can carry a poor long-term prognosis [4]. In children, urological causes of haematuria are so uncommon that initial nephrological referral is widely practised, but the present study confirms that one-third of all adult patients come to nephrologists from urologists, suggesting that urological referral remains the commonest approach in primary health care. The low incidence of urological malignancy in adults under the age of 40 suggests that it might be more appropriate if a nephrologist saw these patients initially [17].

IgA nephropathy is recognised increasingly as a common type of glomerulonephritis in Western countries. Although initially thought to be uncommon in the UK [5], recent data suggest that this is not so and that the incidence is apparently increasing [8, 9]. Rather than a true change in disease frequency, an alternative explanation could be variation in attitudes to renal biopsy for patients with microscopic haematuria.

The present questionnaire confirms a wide range of clinical practice amongst UK nephrologists; 10% had a ‘biopsy score’ greater than 1.75, regarding microscopic haematuria as an almost universal indication for renal biopsy even without proteinuria or intermittent macroscopic haematuria, whereas others were much more conservative and would rarely do a biopsy in the face of normal blood pressure and normal renal function (9% had a ‘biopsy score’ less than 0.75). There was, however, close consensus between paediatric and adult nephrologists in attitudes to biopsy in children; since biopsy scores did not differ between senior registrars and consultants, there was no evidence that the exuberance of youth is overtaken by the wisdom of experience.

A high proportion of patients with microscopic haematuria who may have IgA nephropathy will there-
fore remain undiagnosed with current urological and nephrological practice in many UK centres, and the progressive nature of IgA nephropathy may result in late presentation with renal failure and contracted kidneys.

An alternative strategy is to define, by examining the urine, patients with glomerular disease, thus limiting the requirement for renal biopsy. However, neither of the recently proposed techniques, phase contrast microscopy [18] and Coulter counter analysis [19], was widely practised or found to be of major value by British nephrologists. Renal imaging should be carried out in all cases of haematuria even if glomerular disease is obviously present.

Amongst the range of additional clinical features which respondents felt could modify their decision to take a biopsy, the need to make a definite diagnosis of hereditary nephropathy received particular emphasis, a family history of renal disease with or without deafness endorsing the need for renal biopsy. As well as in families with typical Alport’s syndrome, such an approach will identify other familial nephropathies including thin membrane nephropathy [3]. The urine of first-degree relatives of young patients with haematuria should also be examined. Persistence of haematuria was also regarded, especially among paediatricians, as a feature increasing the likelihood of significant glomerular disease, periods of 6–12 months observation being proposed before biopsy was justified. There is documented evidence that haematuria of more than 6 months duration is of greater prognostic importance in children [20].

Although the absolute incidence of IgA nephropathy remains uncertain, variations in apparent incidence in different units may reflect varying attitudes to renal biopsy, a proposition supported by the positive correlation (p = 0.03) found between ‘biopsy score’ and incidence of IgA nephropathy. Of particular interest are the data from two groups of nephrologists for whom renal histopathological assessment had been provided by a single consultant. These figures allow the elimination of a further potentially confounding factor—the variation in histological and immunofluorescence definition of IgA nephropathy. In these two contrasting groups a low biopsy rate for microscopic haematuria (biopsy score 0.5) and a low incidence of IgA nephropathy (5%) in one unit contrasted with a biopsy score of 1.83 and an incidence for IgA nephropathy of 25% in the other.

Although renal biopsy is a safe procedure with low morbidity and high diagnostic yield in many centres, the findings of this study do not necessarily provide clinical justification for widespread adoption of an aggressive renal biopsy policy in patients with haematuria. However, the differing clinical practices revealed by this study do provide an explanation for our varying perception of the frequency of IgA nephropathy, and other glomerular diseases presenting with haematuria, in the United Kingdom.

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