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Original article

Long-term follow-up of patients with persistent/recurrent, isolated haematuria: a Hungarian multicentre study*

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Abstract. A retrospective multicentre study of 341 children with persistent/recurrent, isolated haematuria is described. The haematuria was isolated for at least 6 months at the beginning of observation. The duration of follow-up was 2–5 years in 201, 5–10 years in 119, 10–15 years in 19, and over 15 years in 2 cases. Of these patients 47.8% became symptom-free. In 18.4% the haematuria remained isolated; in 13.8% it was combined with proteinuria over 250 mg/day more than 2 years later. The occurrence of associated proteinuria increased progressively with time. It was 8.6% between the 3rd and 5th years, and 37.0% after the 5th year. Renal biopsy was performed because of the symptoms of glomerular disease in 47 cases at an average time of 12 months following the appearance of proteinuria. Proteinuria appeared after a 2–5, 5–10, 10–15 and more than 15 years follow-up period in 16, 23, 6, and 2 patients respectively; 14 of them had Alport's nephropathy. The percentage of more serious azotaemia was 1.7 (creatinine clearance: 10–50 ml/min per 1.73 m^2) and 0.3 (creatinine clearance: <10 ml/min per 1.73 m^2). Mortality was 0.58%. Most of the patients who developed severe azotaemia had persistent microscopic haematuria at the beginning. The prevalence of hypertension was only 1.2%. The time of its appearance was above 5 years in 2 and below 5 years in 2 cases. All these patients had chronic glomerulonephritis. The haematuria was associated with hypercalciuria in 19.9%. In 14.3% of the overall group of patients urolithiasis developed 2–15 years after onset. All of these had hypercalciuria. Our findings suggest that symptoms of isolated haematuria may last for a long-term period and need systematic control. When proteinuria and/or hypertension is associated with haematuria a worse prognosis can be expected.

Key words: Haematuria, persistent/recurrent, isolated – Follow-up

Introduction

Persistent and recurrent isolated haematuria is not uncommon in children. It causes very great anxiety for the parents and a diagnostic dilemma for the physician. An extensive list is now available of possible aetiological factors for isolated haematuria. In the event of this single symptom, the questions that arise are: what is the likelihood of a

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poor outcome, and therefore what intensive examinations should the children undergo, including invasive procedures such as radiological, isotope investigations and kidney biopsy? Several clinical and pathological studies have emphasized the benign prognosis, but their follow-up period was short and the number of patients was rather low [1–6]. Other reports found isolated haematuria to be a potentially progressive disease in 25% of the cases [7] or even more, but in the latter studies other signs and symptoms besides haematuria were not strictly excluded.

We report a retrospective multicentre study of 341 children with persistent or recurrent, isolated haematuria followed up over a period of 2–17 years. The aim of the study was to determine the long-term outcome and to estimate the proportion of patients in whom invasive diagnostic methods can be expected to be necessary.

Materials and methods

This study was a retrospective analysis of the long-term follow-up of the patients with isolated haematuria, persisting or recurring for at least 6 months. These children were under the care of 3 university paediatric departments and 19 hospitals between 1 January 1970 and 31 January 1987. The majority of patients (72.5%) originated from the 3 university paediatric departments and 4 larger hospitals but similar cases (27.5%) were collected from 15 other hospitals. The minimum follow-up time was 2 years, the maximum 17 years. The total number of nephrological cases seen in this period was 11,600. Thus these 341 patients with isolated haematuria comprised 2.94% of the overall group of children with kidney or urinary tract diseases. The 341 patients were either admitted with macroscopic haematuria or microscopic haematuria which was observed by chance in the course of a general examination performed because of non-nephrological symptoms. Before the terms persistent or recurrent were assigned, patients were on a monthly regular control. Cases were excluded from the study if they were associated with a urinary tract infection or obstructive uropathies, vesicoureteral reflux or ureter duplication recognized in the first 6 months after the onset of haematuria, or if the haematuria was accompanied by other nephrological symptoms (e.g. proteinuria, hypertension, azotaemia or any sign of systemic disease) less than 2 years after first presentation.

Before they were selected for the study, all patients with isolated haematuria had a nephrological examination and laboratory evaluation. The following definitions were used:

Haematuria: 20 or more RBC/0.9 mm^3 in a counting chamber in a fresh, uncentrifuged midstream specimen. Care was taken not to obtain any samples during or within 3 days after menstruation, and to avoid artificial bleeding from minor mechanical trauma.

Proteinuria: more than 250 mg in a 24-h collection. Quantitative determinations were made by the biuret method.

Urinary tract infection: bacterial growth in a bladder punctured urine sample, or at least 100,000 colonies/ml for any individual organism in two consecutive clean voided midstream specimens.

Blood pressure control and examination of renal function, including endogenous creatinine clearance, quantitative protein and calcium excretion, were performed in all cases. In addition, imaging of the kidney and urinary tract by ultrasound and i.v. urography was carried out in all patients, with I^{125} or I^{131} renography and micturating cystography in suspected cases of obstructive uropathy.

Following an average time of 12 months, kidney biopsy was performed in 47 cases because of the associated symptoms of glomerulonephritis or nephrotic syndrome. For light microscopic studies, besides the usual haematoxylin-eosin, the following staining techniques were used consistently: Jones' silver methenamine; periodic acid-Schiff; Hart's stain; Congo red or gentian violet. Direct immunofluorescence examination was carried out with FITC-conjugated antihuman IgA, G, M, C3, Clq, C4, fibrinogen, albumin, kappa and lambda antisera (Dakopatts Copenhagen, Denmark). For electron microscopic investigation, the freshly removed renal tissue sample was fixed in 2.5% glutaraldehyde for 24 h, then in 1% osmium for 1 h. Audiograms were initially recorded in the patients suspected of having Alport's syndrome, and more recently for all patients. This was also carried out on family members of patients with Alport's syndrome, together with routine urinalysis and blood pressure control.

The data of all selected patients were referred to a working group. The study project was planned and the results were evaluated by these paediatricians.

Results

Clinical features at onset

The type of haematuria in the first 6 months following presentation is shown in Table 1.

At the beginning most patients had recurrent and mixed-type microscopic and macroscopic haematuria. At the time of the first observation of haematuria, the age distribution of the patients was as follows: 2 years, 8.0%; 3 years, 13.9%; 4 years, 16.5%; 5 years, 16.5%; 6 years, 11.3%; 7 years, 7.8%; 8 years, 8.6%; 9 years, 4.6%; 10 years, 6.5%; 11 years, 4.6%; 12 years, 1.9% of all cases. The largest number of patients were in the 3- to 5-year age group. The proportion of boys and girls was 49.3% and 50.6%, respectively.

Follow-up studies

The outcome of the haematuria is presented in Table 2. Of the 341 cases 163 have been symptom-

Table 1. The type of haematuria in the first 6 months

Type of haematuria	Number of cases	(%)
Microscopic	106	(31.1%)
Macroscopic	95	(27.8%)
Micro/macroscopic (mixed-type)	140	(41.1%)
Persistent	137	(40.2%)
Recurrent	204	(59.8%)
Total number of cases	341	(100%)

Table 2. The outcome of haematuria

Follow-up (years)	2–5	5–10	10–15	>15	Total
Patients with isolated haematuria					226 (66.3%)
became symptom-free (>2 years)	90	65	8	–	163 (47.8%)
remained isolated haematuria	43	17	3	–	63 (18.4%)
Patients with hypercalciuria	53	13	2	–	68 (19.9%)
manifested urolithiasis	33	13	2	–	49[a] (14.3%)
Patients with glomerulonephritis					47 (13.8%)
without immunosuppressive treatment	12	11	6	2	31 (9.1%)
with immunosuppressive treatment	4	12	–	–	16 (4.7%)
treated patients with long-term remission (>2 years)	–	9	–	–	9 (2.6%)

[a] Included in the group of patients with hypercalciuria

free for more than 2 years, and in a further 63 children, the haematuria has remained isolated.

Table 2 presents the number of patients exhibiting hypercalciuria (68:19.9%). In 49 (14.3%) of them urolithiasis developed 2–15 years following presentation. This comprised 72.0% of the patients with hypercalciuria. None of them showed any clinical symptoms or signs of stone formation on X-ray film or isotope renography in the first 6 months of observation.

In 47 children a more serious glomerulopathy developed 2–17 years after first presentation. In all of them proteinuria was associated with haematuria more than 2 years after onset (in 16, 23, 6 and 2 cases it happened after 2–5, 5–10, 10–15 and over 15 years following the onset, respectively). In the overall group of patients the proportion of associated proteinuria increased progressively with time: it was 8.6% between the 3rd and 5th years, and 37.0% after the 5th year. The histological diagnosis of these 47 biopsied patients and the results of immunosuppressive treatment are shown in Tables 2 and 3.

Seventeen children had mesangial proliferative glomerulonephritis (MSGN), with variable degrees of histological damage, and 10 patients were diagnosed as having Alport's syndrome on the basis of combined pathological (biopsies studied by electron microscopy) and clinical criteria (familial haematuria, sensorineural hearing loss, progression of renal failure). Four further children exhibited basement membrane changes typical or suggestive of Alport's syndrome, and haematuria was found among their first-degree relatives, but these patients and their family members did not display a sensorineural hearing loss or other suggestive features. In these latter cases the diagnosis of Alport's syndrome will probably be confirmed in the future. Three patients had IgA nephropathy and 5 focal proliferative glomerulonephritis (FPGN).

Sixteen children with a picture of chronic glomerulonephritis or who subsequently developed nephrotic syndrome were treated with immunosuppressive therapy. Histologically, these cases corresponded to MSGN (n = 8); membranoproliferative glomerulonephritis (MPGN) (n = 3); membranous glomerulonephritis (MGM) (n = 2); focal segmental glomerular sclerosis (FSGS) (n = 1); or minimal change nephrotic syndrome (MCNS) (n = 2) (in the first 6 months these 2 patients had isolated microscopic haematuria, which was associated with proteinuria subsequently). During the treatment 9 children became symptom-free (2 MCNS, 2 MGN and 5 MSGN cases), but in 1 patient with FSGS end-stage renal failure developed and regular haemodialysis was started subsequently. In 6 further patients (3 MPGN, 3 MSGN), the proteinuria and haematuria did not change. Two of them displayed a markedly decreased (10–50 ml/min per 1.73 m^2), and one a moderately decreased (50–75 ml/min per 1.73 m^2) creatinine clearance (Table 3). Four patients (1.2%) had hypertension. The time of ap-

Table 3. Histological diagnosis of glomerulopathies examined by biopsy

Histological diagnosis	Number of cases
MCNS	2
FPGN	5
MSGN	17
MPGN	3
MGN	2
FSGS	1
IgA-GN	3
Hereditary or Alport's nephropathy	14

MCNS = Minimal change nephrotic syndrome; FPGN = focal proliferative glomerulonephritis; MSGN = mesangial proliferative glomerulonephritis; MPGN = membranoproliferative glomerulonephritis; MGN = membranous glomerulonephritis; FSGS = focal segmental glomerulosclerosis; IgA-GN = IgA nephropathy

Table 4. The incidence of azotaemia and mortality in patients with isolated haematuria

Follow-up (years)	2–5	5–10	10–15	>15	Total (%)
Azotaemia					
creatinine clearance <10 ml/min/1.73 m²	1	–	–	–	1 (0.3%)
10–50 ml/min/1.73 m²	1	4	–	1	6 (1.7%)
50–75 ml/min/1.73 m²	21	4	3	1	29 (8.5%)
Died		2			2 (0.58%)

pearance was 2–5 years in 2; 5–10 years in 1; and over 15 years in 1 case. Two patients had MPGN, 1 had MSGN and 1 FSGS.

The incidences of azotaemia and mortality among the patients are listed in Table 4. It seems to be very important that in 23 of the 36 cases with azotaemia, the creatinine clearance decreased during 2–5 years after the appearance of haematuria, while in the remaining minority of the patients it developed later. In 6 patients with a creatinine clearance of less than 50 ml/min per 1.73 m², the haematuria was due to glomerulopathy. Three children had Alport's syndrome, and 3 had therapy-resistant nephrotic syndrome. In 1 case with a solitary kidney haemangioblastoma developed. This child and another patient with Alport's syndrome died because of a serious intercurrent infection (Table 4).

Apart from the children with renal failure, growth was normal and the blood pressure for age was normally distributed except for those noted as being hypertensive.

Early prognostic features of patients with severe azotaemia

Five of 7 children with severe azotaemia (creatinine clearance <50 ml/min per 1.73 m²) had persistent microscopic or persistent mixed-type haematuria at onset. In four, this was associated with proteinuria (>0.5 g/day >2 years following first presentation) and 1 patient had hypertension later on (>150/100 mmHg). One patient with recurrent macroscopic haematuria had a haemangioblastoma in his solitary kidney. Another child with macroscopic haematuria improved later.

Discussion

The proportion of our patients with persistent or recurrent, isolated haematuria among the total nephrological cases is not very high (3.02%) but, considering the unknown underlying disease and the final outcome, the attention that must be paid to these children is not insignificant. Although we found a low mortality in our series, the final prospects for these patients are less favourable than that for cases found in a haematuria screening programme [8], particularly in view of the high percentages of azotaemia (10.5%) and severe glomerulopathies (13.8%). The explanation could be that the patients were referred to the hospital on account of a macroscopic haematuria, or the findings of microscopic haematuria were obtained by chance in connection with a general examination carried out because of a suspected non-nephrological disease. Although the creatinine clearance decreased in the first 5 years, the duration of follow-up is important in respect of the changes in morbidity and potential mortality. It is very likely that the possibility of morbidity and mortality will increase in certain adolescent boys with Alport's syndrome or in the therapy-resistant glomerulopathies of immunological origin.

The number of cases with IgA-nephropathy was only 3 of 47 patients who underwent renal biopsy. This probably does not represent the occurrence of Berger's disease in the whole paediatric population but, more likely, the prevalence of IgA-GN amongst the more serious glomerulopathies, which appeared as isolated haematuria in the beginning. The proportion of patients who developed urolithiasis in the hypercalciuria group was 72%.

The population served by our 19 hospitals and 3 university paediatric departments is approximately 8 million. In this respect our series is comparable with the study of 100 patients reported by Miller et al. [9]. In Hungary the patients with persistent, recurrent haematuria are almost exclusively under hospital management, and therefore the number of our cases probably closely reflects the true proportion of these patients in the overall population (43.75/1 million). In spite of the higher number of our patients, we had only 1 patient with FSGS who developed end-stage renal failure (0.3%), and 2 other children with a medium degree of azotaemia who died (one with Alport's syndrome and another with haemangioblastoma combined with unilateral renal agenesia). The mortality was 0.58%. The incidence of hypertension

requiring treatment was also lower (1.2%) than among the patients of Miller et al. [9]. From a nephrological point of view, therefore, the fate of our patients at present seems to be more favourable than in the above-mentioned study. Nevertheless, we had 4 other children with an appreciably (10–50 ml/min per 1.73 m^2) and a further 29 with a moderately (50–75 ml/min per 1.73 m^2) decreased creatinine clearance. The final fate of these children and those with various kinds of glomerulopathy will only emerge over a longer period. In any event, the occurrence of associated proteinuria increases progressively with time (8.6% in the first 5 years, 37.0% after 10 years).

In a considerable percentage of the children (14.3%), the haematuria proved to originate from urolithiasis. As most of these urolithiasis diagnoses were made in the 2nd-5th years, it is very likely that these stones were present in a non-visualizable size at the time of admission, and grew slowly in the following years. These stone-forming cases are partly included in the larger group of patients with hypercalciuria (19.9%), which may also be responsible for isolated haematuria. Nevertheless, none of these children developed hypertension or a marked decrease in creatinine clearance. We observed that most patients with relatively severe azotaemia had persistent microscopic haematuria (5 of 7) with or without intermittent macroscopic haematuria at presentation.

In the cases in which proteinuria accompanied the haematuria, histological examination showed an advanced glomerular lesion. Hypertension was a very rare complication of isolated haematuria, and kidney tumour occurred extremely infrequently among the underlying disease.

To summarize, the prognosis of persistent/recurrent, isolated haematuria is fairly good, but the final outcome in most cases may be predictable only after a long-term follow-up. In some patients, urolithiasis can be discovered several years following the appearance of haematuria. Persistent microhaematuria in the beginning, with or without episodes macrohaematuria, and associated proteinuria and/or hypertension in the following period suggest a worse prognosis; these complications indicate the need for histological examinations. Intermittent microscopic haematuria rarely leads to chronic renal failure. Intermittent haematuria may be associated with an intermittent insult, with periods of repair in between, while persistent haematuria is likely to be associated with a continuing pathological process. In suspected cases of Alport's syndrome, the examination of family members, including audiometry, may be helpful but an accurate diagnosis can be reached only by electron microscopy. The most obvious way to reduce the number of slowly deteriorating and unexpectedly uraemic cases is early hospital examination and long-term follow-up with appropriate treatment as soon as possible.

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