Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 22 (1–2), pp. 71–76 (1981)

Haematuria: Glomerular or non-glomerular? Urinary protein fractions in monosymptomatic haematuria

By

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(Received November 25, 1980)

The pattern of the physiological proteinuria determined with SDS-polyacrylamide-gel-electrophoresis, is altered by haematuria even in the absence of proteinuria. Monosymptomatic haematuria due to glomerular diseases is linked with selective glomerular proteinuria, while haematuria of urinary tract origin is accompanied by the complete spectrum of serum proteins. The characteristic protein patterns are of diagnostic value in the differential diagnosis of isolated haematuria: glomerular or non-glomerular.

Monosymptomatic haematuria (MH) is a haematuria without any sign of other renal impairment and in absence of other pathological urinary findings, "in absence of proteinuria". MH is a common problem in paediatric nephrology. It can occur as a short episode in febrile conditions after strenous physical efforts or as a toxic reaction to some drugs. MH lasting several months or years may occur in renal, urinary tract and in systemic diseases, as shown in Table I.

Diagnostic problems arise in cases of MH if the cause of the haematuria is uncertain. Is it a sign of a glomerular process: benign recurrent haematuria, IgA mesangiopathy? — or is it caused by a small, undetectable stone or teleangiectasia. If we can be certain that it is of glomerular origin, as in most cases in children, so further invasive diagnostic methods such as cystocopy, retrograde pyelography, aortography or renal biopsy, are not necessary.

The term "haematuria in absence of proteinuria" is, however, not correct. Healthy men have physiological proteinuria. Is it not altered by haematuria even in cases when the concomitant urinary protein output is so slight that it remains undetected with insensitive routine screening methods?

The aim of this study was to investigate the urinary protein fractions of patients suffering from MH of renal and of urinary tract origin.

Material and Methods

Patients. Urinary protein concentration and fractions were investigated in 19 children suffering from MH. Gross haematuria was present in 4 cases of glomerular and 3 cases of urinary tract haematuria. Protein

TABLE I

A. Renal haematuria

1. Glomerulonephritis:

(i) secondary to specific diseases: postinfectious, Schönlein-Henoch nephritis, juvenile rheumatoid arthritis, SLE, Alport syndrome, shunt nephritis, subacute bacterial endocarditis
(ii) Polycystic kidney disease
(iii) Renal neoplasm, renal tuberculosis, renal haemangioma and teleangiectasia
(iv) renal vein thrombosis
(v) IgA mesangiopathy
(vi) Essential or benign recurrent haematuria

2. Interstitial nephritis:

(i) Diffuse — toxic, metabolic, allergic, hereditary
(ii) Localized — VUR, infection

B. Urinary tract haematuria:

Hydronephrosis, meatal stenosis, urinary tract infection
Foreign body, tumour, trauma
Lithiasis

C. Systemic diseases:

Haemorrhagic diathesis, secondary intravascular coagulopathy
Sickle cell disease

concentration in these urines was 370—670 mg/l, and so "proteinuria" was diagnosed by the routine screening methods. In the other 23 urine samples the haematuria was of lesser degree, with 25—40 RBC in the sediment. Protein concentration in these urines was 115—275 mg/l, thus these were cases of "haematuria in absence of proteinuria".

Ten children had glomerular disease according to renal biopsy done at 11—19 month of MH. Histology showed in 3 cases

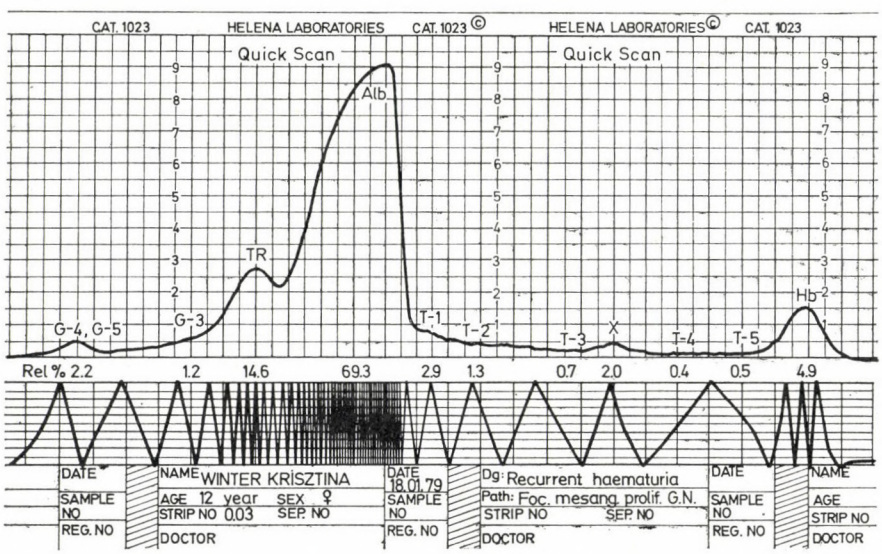

FIG. 1. Glomerular haematuria. Diagnosis: benign recurrent haematuria. Histology: Focal mesangial proliferation; IgG and C' deposits

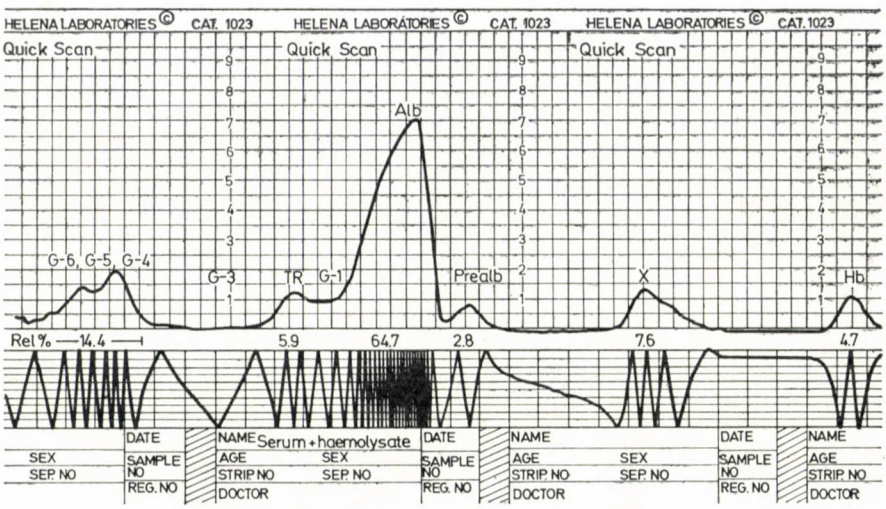

FIG. 2. Serum-haemoglobin standard

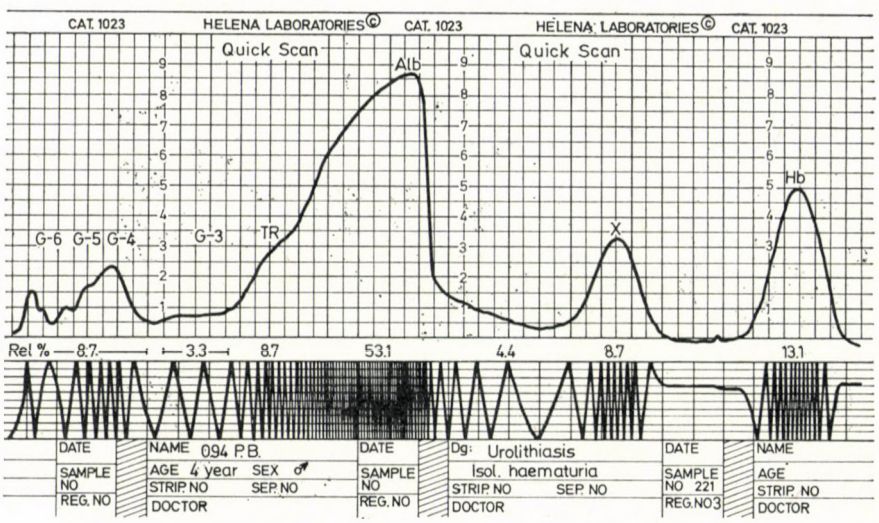

FIG. 3. Urinary tract haematuria. Diagnosis: Nephrolithiasis

minimal glomerular alterations, in 4 cases IgA mesangiopathy [2] and in 4 cases focal or diffuse mesangial proliferation with IgG and C' deposits.

Eight patients suffered from nephrolithiasis. The stones were detected at the first haematuric episode in 3 cases; in 5 cases the MH lasted for 4—10 months before diagnosis.

One patient suffered from abacterial interstitial nephritis. Diagnosis was based on renal histology 14 months after the onset of MH.

Serum-haemoglobin standard. As reference material we used a standard serum-haemoglobin preparation. Pooled serum of 14 healthy children was mixed with a haemoglobin (HbA) solution. Final concentration

of the standard was 38.2 g/l serum protein and 16.7 g/l HbA.

Urine collection Voided urine samples were investigated. Urine was buffered with neutral buffer and conserved with sodium azide [10].

Urinary total protein concentration was determined by the method of Yatzidis [12].

Urinary protein fractions were separated by sodium-dodecylsulphate acrylamide-gel disk-electrophoresis. The nomenclature of Boesken et al. [5] was applied.

Quantitative estimation was done from scans obtained by a Quick Scan Jr. densitometer and integrator equipment of Helena Laboratories, filter 595 nm.

Urinary protein fractions are summarized as follows:

High mol wt globulins: the globulin fractions G6, G5, G4 and G3, proteins of 1,000,000 to 100,000 dalton mol wt.

Middle mol wt proteins: transferrin, G1 and albumin, from 89,000 to 69,000 dalton mol wt.

Low mol wt microproteins: the "tubular microproteins" T1—T5, from mol wt 52,000 to 10,000.

Haemoglobin, as a monomer in the fastest band in the gel.

Fraction X, a protein with a mol wt of about 30,000 dalton, near to fraction T3. The nature of this protein, occurring in haemoglobinuric urines is uncertain [6]. We suggest that it is an artificial haemoglobin derivative, haemoglobin dimer.

Results

In MH caused by glomerular processes we found selective glomerular proteinuria. The proportion of albumin and transferrin was high in relation to the high mol wt globulins (Fig. 1).

The urinary protein pattern in MH due to nephrolithiasis was very close to the fractions of the serum + haemoglobin preparation. The proportion of middle mol wt proteins to high ml wt globulins was similar as the fractions of the serum (Figs 2 and 3)

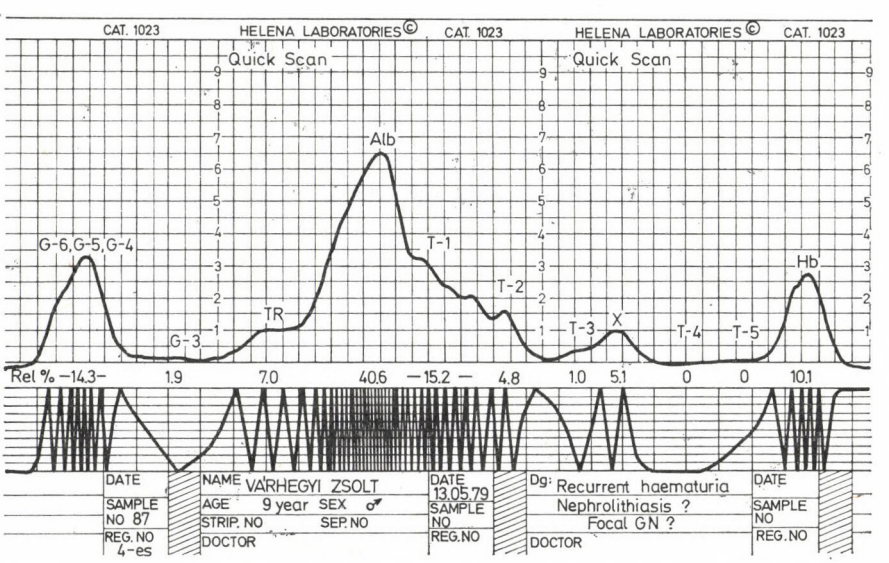

Fig. 4. Urinary tract haemoglobinuria + tubular proteinuria. Diagnosis: Abacterial interstitial nephritis. Histology: Peritubular and periglomerular proliferation

TABLE II

Urinary protein fractions in monosymptomatic haematuria

No. of patients, Diagnosis	Urine sample N	High mol wt globulins	Middle mol wt proteins	Low mol wt microproteins	Fraction X	Haemoglobin	Middle mol wt / High mol wt
10 Glomerulonephritis	14 mean	5.2	83.2	4.8	1.8	5.0	16.0*
	range	2.4—12.5	72.5—90.7	2.7—8.1	0—4.6	2.8—8.1	7.8—38.7
1 Interstitial nephritis	3 range	13.7—16.2	47.6—53.8	19.2—27.1	3.8—5.1	6.7—10.1	3.9—5.8
8 Urolithiasis	13 mean	14.2	53.4	5.6	7.6	10.1	4.4*
	range	10.0—18.6	53.4—59.0	4.1—7.8	1.5—11.6	4.8—15.6	2.9—5.9

*between the two means, $p < 0.01$

The ratio middle mol wt proteins: high mol wt globulins differed significantly in the two groups of patients.

The concentration of fraction X in relation to haemoglobin was higher in urinary tract haematuria than in glomerular haematuria. These results have not yet been evaluated statistically.

In one case of MH due to abacterial interstitial nephritis, the urinary protein pattern was similar to the urinary tract haematuria and in addition there was a marked tubular proteinuria (Fig. 4).

Results are summarized in Table II.

DISCUSSION

MH is a frequent condition in childhood. The pathological process resulting in isolated haematuria often remains uncertain. The cause of the persistent or recurrent haematuria was unknown in about 40% of the cases of Mehls et al. [9] as well as in our patients.

The main diagnostic problem is whether the haematuria is of glomerular origin, a benign recurrent haematuria [1, 4, 7, 8,] or a urinary tract bleeding caused by an undetected stone or some other process. The complete diagnostic procedure would include intensive urological exploration (with retrograde pyelography, cystoscopy, aortography) and/or renal biopsy, but we avoid these invasive methods in most of the cases.

An approach to differentiation is a morphological examination of the sediment [3, 12]. Glomerular haematuria gives rise to a wide range of morphological alterations in the red cells with the presence of casts. In contrast, urinary tract bleeding is usually associated with undamaged red cells with a normal haemoglobin content, or with ghosts: red cells normal in shape but containing no haemoglobin.

Another possibility for differential diagnosis can be the analysis of uri-

nary proteins. Boesken [6] reported that postrenal haematuria is characterized by the presence of serum proteins, haemoglobin monomer, and an unidentified protein called protein X fraction. He suggested that the presence of this protein indicated postrenal bleeding.

The present results partly confirm the findings of Boesken; in cases of urinary tract bleeding we have found the same characteristic urinary protein pattern. On the other hand, glomerular haematuria was characterized by selective glomerular proteinuria, but we found beside the haemoglobin monomer also the protein X fraction in glomerular haematuria. The nature of this protein must be clarified; we assume that it is an artificial haemoglobin derivative.

In the present patients, the diagnosis of haematuria was based on renal biopsy or on the detection of renal stones. A further study in unselected patients is needed to establish the routine diagnostic value of the above findings.

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