

FREQUENCY AND GLOMERULAR OR POST-GLOMERULAR ORIGIN OF HEMATURIA IN BRAZILIAN PATIENTS WITH SICKLE CELL SYNDROMES

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ABSTRACT

The occurrence of hematuria was investigated prospectively and retrospectively in a sample of 50 adult patients with sickle cell anemia, hemoglobin SC disease or S/β -thalassemia. The glomerular or post-glomerular origin of hematuria was determined by the investigation of erythrocyte dysmorphism.

During a follow-up period of one year, one or more episodes of hematuria occurred in 11/50 of the patients and the glomerular origin of this manifestation was recognized in 2/10 of all cases. Patients with glomerular damage presented continuous hematuria, whereas patients with post-glomerular damage presented episodic hematuria. The frequency of hematuria did not differ significantly between SS and SC patients or between patients with sickle cell disease and a general control sample from the same hospital. Previous episodes of hematuria confirmed by laboratory tests occurred in 18/50 cases, although they varied with follow-up time.

INTRODUCTION

The incidence and physiopathogeny of hematuria in sickle cell syndromes are controversial (Serjeant, 1974; Humphreys and Allen, 1986). Although most cases of hematuria in patients with hemoglobin S are attributed to damage to the renal medulla, hematuria can also appear in these patients in association with renal papillary necrosis, bleeding from the lower portion of the ureter, ulcerative damage to the bladder, and priapism (see Marguilies and Minkin, 1969; Serjeant, 1974; Minkin *et al.*, 1979; Asnes *et al.*, 1983; Oksenhendler *et al.*, 1984; Bahnson, 1987; Quinib, 1988, among others). Furthermore, the role of the various glomerular changes reported to

occur in sickle cell disease as factors inducing hematuria is also controversial (Walker *et al.*, 1971; Buckalew and Someren, 1974; Morgan and Serjeant, 1981).

In the present study, the incidence of hematuria was investigated in a sample of patients with sickle cell disease and compared with that observed in a control sample from the same hospital. The glomerular or post-glomerular origin of this clinical manifestation was studied simultaneously.

CASES AND METHODS

A prospective and retrospective investigation was conducted on 50 adult patients with sickle cell syndromes (35 patients with homozygous sickle cell anemia, 10 patients with heterozygous hemoglobin SC disease and 5 patients with heterozygous S/ β -thalassemia) regularly followed at the University Hospital of UNICAMP. Patient age ranged from 18 to 52 years (mean \pm SD = 28.81 \pm 8.38 years).

In the prospective study, the occurrence of hematuria was investigated over a period of one year by collecting at least one urine sample per month from each patient into a sterile container. The urine samples from female patients were collected outside the menstrual period.

The samples were immediately transported to the Clinical Pathology Laboratory of UNICAMP and submitted to routine urinalysis (urine I) (Vallada, 1988). When hematuria was detected, its glomerular or post-glomerular origin was determined on the basis of the presence or absence of erythrocyte dysmorphism (Birch and Fairley, 1979; Fairley and Birch, 1982; Fasset *et al.*, 1982; Birch *et al.*, 1983). As a safety measure, the presence of erythrocyte dysmorphism was not investigated in urine sediments presenting a number of red blood cells of less than 5000/ml (Cuellar-Cabrera and Hernandez, 1985).

Hematuria was considered to actually be due to hemoglobin S, after excluding the possibility of a random association between the two by clinical and laboratory tests carried out by specialized personnel at the University Hospital of UNICAMP.

For the retrospective study, the clinical and laboratory antecedents recorded for the patients during follow-up, before the initiation of the present study, were investigated from medical records.

In parallel with the study of the sickle cell patient sample, routine urinalysis data for 495 patients seen at the University Hospital of UNICAMP were surveyed. These patients (391 Caucasians and 104 Blacks), matched for age range, sex and socioeconomic level with the patients with hemoglobin S, were investigated to determine the frequency and probable clinical diagnosis of hematuria in the hospital in which the study was conducted. Cases of traumatic hematuria (after renal surgery,

after delivery, after bladder catheterization etc.) were excluded from the hospital sample.

Data were analyzed statistically by the chi-square test, with the level of significance set at 5%. When necessary, Yates correction and/or confirmation by the Fisher test were performed.

RESULTS

Of the 50 patients with sickle cell syndromes studied, 11 manifested at least one episode of hematuria during the course of the present study. Except for hemoglobin S, these patients had no clinical alterations such as arterial hypertension, urinary infection, calculi, diabetes, etc. to which hematuria could be attributed.

When the sample was classified by hemoglobin genotype, the presence of hematuria was detected in 9/35 of the patients with sickle cell anemia, 2/10 of patients with heterozygous SC and in no patient with S/ β -thalassemia. Frequency of hematuria did not differ significantly among the three sickle cell syndromes studied (corrected $\chi^2_{(2)} = 1.715$; $P = 0.42$). Again, the incidence of hematuria did not differ significantly when patients with sickle cell anemia were compared to patients with hemoglobin SC disease ($\chi^2_{(2)} = 0.1375$; $P = 0.71$; Fisher test = 0.778). The occurrence of hematuria did not vary with sex or age range.

Of the 11 patients with hematuria, only one had a number of red cells/ml urine of less than 5000, six had values between 5000 and 100,000, and four had red cell percentages higher than 100,000/ml. Two patients revealed continuous hematuria throughout the one-year follow-up, six had only one isolated episode, and three had two or more episodes of hematuria. The presence of erythrocyte dysmorphism indicating the glomerular origin of hematuria was detected in only two of the 10 patients who presented hematuria of more than 5000 red cells/ml urine, one of them being a female patient with sickle cell anemia and the other a female patient with hemoglobin SC disease, aged 21 and 28 years, respectively. It is interesting to note that both had continuous hematuria. Figures 1 and 2 respectively illustrate normal and dysmorphic red cells detected in the urine sediment.

Taking into consideration the clinical history of the patients, the presence of at least one episode of hematuria confirmed by laboratory tests was detected in 18 of the 50 patients examined. This positive history of hematuria was detected in 11/35 of the patients with sickle cell anemia, in 5/10 of the patients with heterozygous SC and in two of the five patients with S/ β -thalassemia. Also, the incidence of a positive history of hematuria did not differ significantly between patients with homozygous SS and patients with heterozygous SC ($\chi^2_{(1)} = 1.17$; $P = 0.279$). However, it should be pointed out that the frequency of a positive history of hematuria varied significantly

with follow-up time among patients with sickle cell syndromes, being detected in 8/33 of the patients with less than five years of hospital follow-up, in 8/15 of patients with 10 to 15 years of follow-up and in the two individuals who have been followed for more than 10 years at the University Hospital of UNICAMP.

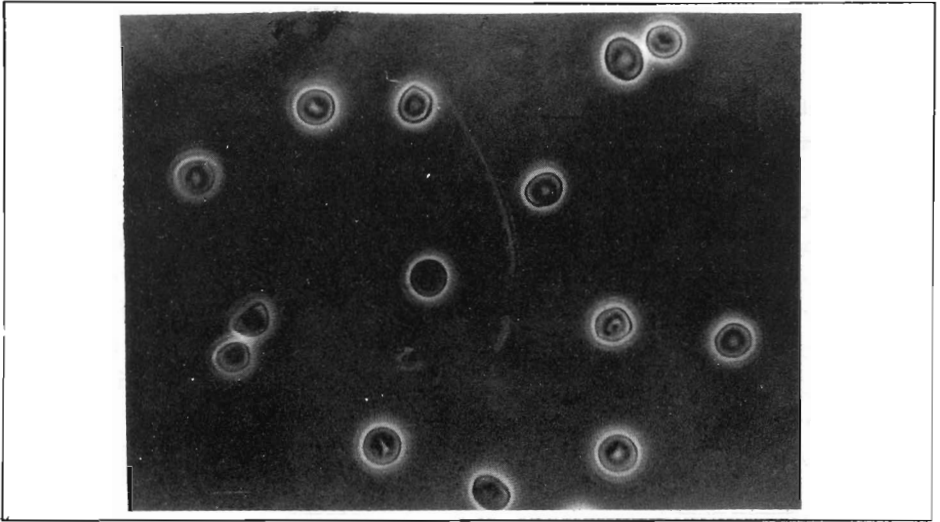


Figure 1 - Normal red blood cells with no dysmorphism in the urine sediment. (Phase contrast microscopy, 400X).

Analysis of the data obtained for the control sample showed that 70/495 of the patients examined had hematuria. The incidence of hematuria among Black patients (18/104) did not differ significantly from that among Caucasians (52/391) or ($\chi^2_{(1)} = 1.087$; $P = 0.297$). Of these 70 patients with hematuria, 22 had urinary infections, seven nephritis associated with polyarteritis, six arterial hypertension, six urinary calculi, five fever-inducing diseases, four lupus-induced glomerulonephritis, three pyelonephritis, three glomerulonephritis induced by polyarteritis nodosa, three nephritis induced by bacterial endocarditis, two chronic renal insufficiency, two diabetic glomerulosclerosis, one pre-eclampsia, and six hematuria of unelucidated etiology.

Thus, the incidence of hematuria in the sample of patients with sickle cell disease (11/50) did not differ significantly from that observed in the general hospital sample (70/495) ($\chi^2_{(1)} = 2.22$; $P = 0.136$). However, the incidence of a positive history of hematuria was significantly higher among sickle cell patients (18/50) than among control subjects (corrected $\chi^2_{(1)} = 14.45$; $P = 1.44 \times 10^{-4}$).

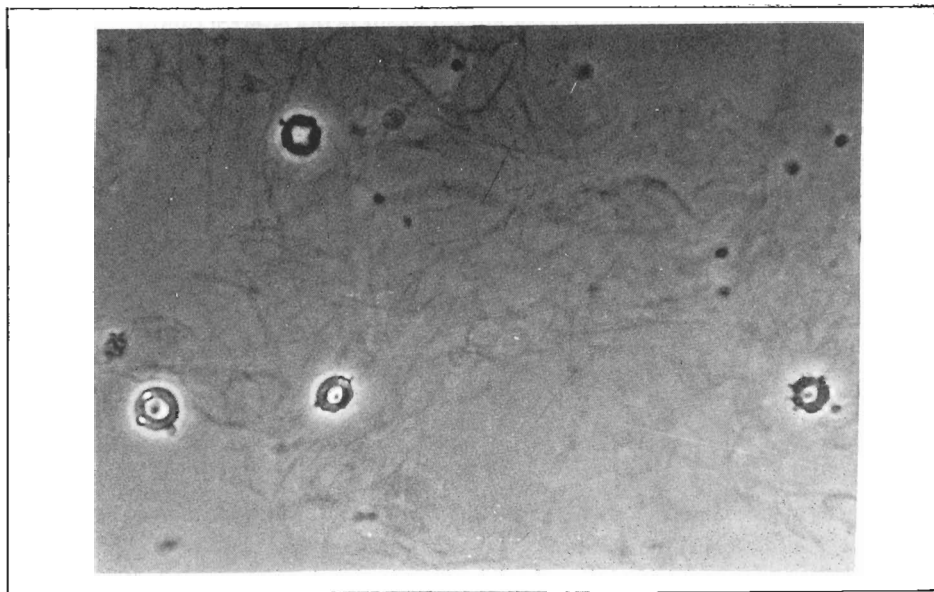


Figure 2 - Dysmorphic red blood cells in the urine sediment. (Phase contrast microscopy, 400X).

DISCUSSION

The significant proportion of patients (11/50) who manifested hematuria during the study period emphasizes the importance of this clinical manifestation in sickle cell syndromes. However, the fact that its incidence among sickle cell patients did not differ significantly from that observed in the control sample indicates that hematuria cannot be considered to be a clinical sign suggesting the diagnosis of sickle cell syndromes in our population, as is the case, for example, for osteoarticular pain (Gonçales and Ramalho, 1985; Ramalho, 1986; Gomes and Ramalho, 1989) and for leg ulcers (Ramalho *et al.*, 1985). On this basis, if the interaction with other conditions causing hematuria had not been excluded in the patients examined, the possibility of random association between hemoglobin S and hematuria could not have been ruled out.

Furthermore, by analyzing the most frequent causes of hematuria in the hospital sample, it may be deduced that sickle cell syndromes are of relatively little importance as factors causing hematuria in our population and should be included in the 8.5% of cases of unelucidated etiology together with tumors and other causes. On

the other hand, if hemoglobin S were indeed a considerably frequent cause of hematuria in our population, its incidence among Black patients should be significantly higher than among Caucasians, which did not occur in the control sample examined in the present study.

Although a greater prevalence of hematuria among patients with heterozygous SC and AS than among patients with homozygous SS has been suggested in the literature (Serjeant, 1974), this was not the case in the present sample. Indeed, in addition to the lack of significant differences in hematuria incidence between patients with homozygous SS and patients with heterozygous SC, the frequency of hematuria observed among patients with sickle cell anemia (9/35) was significantly higher than that reported by Ramalho *et al.* (1978) for subjects with sickle cell trait from the same geographic region (4/73) (corrected $\chi^2_{(1)} = 7.33$; $P < 0.01$). According to Serjeant (1974), the greater proportion of AS and SC heterozygotes in samples of sickle cell patients with hematuria may be attributed to the greater prevalence of AS heterozygotes in populations, and to greater survival of SC homozygotes than SS homozygotes.

The proportion of cases with hematuria recorded in the clinical history of patients with sickle cell anemia examined in the present study (11/35) was significantly higher than that reported by Hutz (1981) for Rio de Janeiro patients (33/405) (corrected $\chi^2_{(1)} = 16.8$; $P < 0.001$). Similarly, the frequency of a positive history of hematuria among the patients with heterozygous SC examined in the present study was significantly higher than that reported by Gomes and Ramalho (1989) for SC patients of the same population (3/35) (corrected $\chi^2_{(1)} = 4.37$; $P < 0.05$). These comparisons, however, should be interpreted with caution since the frequency of hematuria calculated from retrospective data has some limitations. Thus, for example, the present study proved that the frequency of a history of hematuria varies significantly with time of patient follow-up.

Finally, the present data indicate that the post-glomerular origin of hematuria should indeed be the most frequent in sickle cell syndromes since 8/10 of the patients examined did not present erythrocyte dysmorphism. However, it is important to emphasize the continuous characteristic of the hematuria presented by the two patients found to have glomerular damage, which was accompanied by also continuous proteinuria. In addition, hematuria caused by glomerular damage may also occur at a higher frequency among older patients with sickle cell disease when a greater proportion of cases of erythrocyte dysmorphism would be expected to occur. In this respect, it is important to remember that glomerular function, although notably preserved in young sickle cell patients (De Jong *et al.*, 1980; De Jong and Van Eps, 1985), begins to be impaired at 40 years of age and may progress to renal failure in some patients (Morgan and Serjeant, 1981).

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RESUMO

A ocorrência de hematúria foi investigada prospectiva e retrospectivamente em uma amostra de 50 pacientes adultos, portadores de anemia falciforme, hemoglobinopatia SC ou S/ β -talassemia. A origem glomerular ou pós-glomerular da hematúria foi determinada pela investigação do dismorfismo eritrocitário.

Durante um ano de seguimento, constatou-se a ocorrência de um ou mais episódios de hematúria em 11/50 (22%) dos pacientes, sendo a origem glomerular dessa manifestação reconhecida em 2/10 (20%) dos casos. Os pacientes com lesão glomerular manifestaram hematúria contínua, enquanto que aqueles com lesão pós-glomerular manifestaram hematúria episódica. A frequência de hematúria não diferiu significativamente entre os pacientes SS e SC, nem entre os falcêmicos e os pacientes de uma amostra geral controle do mesmo hospital. Episódios antecedentes de hematúria confirmada laboratorialmente foram verificados em 18/50 (36%) dos casos, variando, no entanto, com o tempo de seguimento ambulatorial.

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