

Hematuria in Patients With Beta-Thalassemia Major

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Keywords. beta-thalassemia,
proteinuria, urinalysis,
deferoxamine, iron overload

Introduction. Our information about renal involvement in beta-thalassemia major is limited. Recently, few studies have reported proteinuria, hypercalcuria, phosphaturia, and oversecretion of tubular damage markers; however, hematuria has not yet been meticulously studied in these patients. We investigated hematuria in patients with beta-thalassemia major.

Materials and Methods. Urinalysis was performed in 500 patients with beta-thalassemia major under a regular blood transfusion program. In those with hematuria (at least 3 to 5 erythrocytes per high-power field) a second urinalysis was done at the next transfusion time.

Results. The patients ranged in age from 6 months to 32 years. The male-female ratio was 1.05:1. Hematuria was detected in 55 (10.6%), including 9.8% of those younger than 20 years and 20.0% of those older than 20 years. Hematuria was persistent in 79.2% of the second urinalyses. Sixty-four percent of the patients with hematuria were females. A blood transfusion program had been started during the first year of life in 81% percent of the patients with hematuria. Sterile pyuria was detected in 4% and proteinuria in 16% of the patients with hematuria, while these figures in patients without hematuria were 2.1% ($P = .56$) and 1.4% ($P = .002$), respectively.

Conclusions. We found that in patients with beta-thalassemia major, the risk of hematuria rises with age. Moreover, proteinuria seems to be more common in those with hematuria. Further studies are needed to ascertain the importance of these findings.

IJKD 2010;4:133-6
www.ijkd.org

INTRODUCTION

Beta-thalassemia major is one of the most common hereditary hematologic disorders characterized by severely impaired β -globulin synthesis. Profound anemia and excess iron deposition leads to dysfunction of cardiovascular, reticuloendothelial, and other organ systems.¹ However, little information is available about renal involvement in this disease. In the recent years, few studies have demonstrated proteinuria,

aminoaciduria, hypercalciuria, phosphaturia, magnesiuria, hyperuricosuria, low urine osmolality, and excess urinary secretion of markers of tubular damage such as N-acetyl-D-glucosaminidase in patients with beta-thalassemia major.²⁻⁴ Although hematuria is an important urinary finding, it is not yet scrupulously looked for in such patients; therefore, this study was carried out to find the prevalence of hematuria in patients with beta-thalassemia major.

MATERIALS AND METHODS

Five hundred patients (256 men and 244 women; male-female ratio, 1.05:1) with beta-thalassemia major were studied. They were receivers of blood transfusion on a regular basis at Transfusion Center of Shiraz University of Medical Sciences, which is the referral center for such patients in south of Iran. The patients were included in this study by cluster sampling. Clinical diagnosis of beta-thalassemia major in all of the patients was confirmed by hemoglobin electrophoresis. Most of the patients were receiving blood transfusion at 4-week intervals; however, few patients received blood transfusions at shorter intervals. Injection of deferoxamine (20 mg/kg/d to 30 mg/kg/d) was routinely started for the patients aged 3 years or more. This cross-sectional study was completed during a 6-month period.

The patients or their parents were interviewed and a questionnaire was filled, which covered data on age, gender, age at the onset of blood transfusion, deferoxamine use, urinary symptoms, menstruation at the time of study, hypertension, diabetes mellitus, family history of thalassemia syndromes, hematuria, and kidney diseases, such as urinary calculi, glomerular diseases, tubular disorders, and kidney failure. Complete physical examination was performed for all of the patients. Urinalysis was performed for all, except those with menstruation at the time of study; in such patients, urine sampling was postponed to the next transfusion time. All urine samples were collected from the first morning urine, while all patients were fasting and afebrile.

Hematuria was defined as at least 3 to 5 erythrocyte per high-power field in fasting first morning urine in all age groups.^{5,6} Any patient whose urinalysis showed 3 or more erythrocytes had the urinalysis repeated at the next transfusion time. Pyuria was defined as 5 or more leukocytes per high-power field,⁷ and proteinuria, as at least 1+ by urinary dipstick. Ultrasonography of the kidneys and urinary tract was performed for those with persistent hematuria in their 2nd urinalysis.

The *z* test was used to compare the incidence of hematuria in different age groups and also in those with or without proteinuria and pyuria. *P* values of less than .05 were considered significant.

RESULTS

The patients ranged in age from 6 months to 32 years (mean, 14.2 years); 143 patients (28.6%) aged less than 10 years, 307 (61.4%), 10 to 20 years, and 50 (10.0%) over 20 years. None of the patients had any urinary symptoms at the time of the study. All the patients had normal blood pressure. Family history was negative for hematuria or kidney diseases, except for 3 siblings with beta-thalassemia from 1 family and 2 from another one, all of whom had hematuria.

Hematuria was detected in 53 of 500 patients (10.6%), 34 females and 19 males (male-female ratio, 0.55:1). Hematuria persisted in the second urinalysis in 42 of 53 patients (79.2%). On ultrasonography of the kidneys and urinary tract of patients with persistent hematuria, no specific finding related to the causes of hematuria was detected. The frequency of hematuria was 9.8% in those younger than 20 years and 20.0% in older patients; it was not significantly different between the patients in their 1st and 2nd decades of life (*P* = .66), but it was significantly more common in patients older than 20 years (*P* = .04).

Pyuria and proteinuria were also detected in 5 (9.4%) and 9 (16.9%) patients with hematuria, respectively, while among patients without hematuria, pyuria and proteinuria were seen in 2.1% (*P* = .56) and 1.4% (*P* = .002), respectively. None of the possible causes of false-positive proteinuria, such as highly concentrated urine, gross hematuria, or very high urine pH (7 or more), were detected in the patients. Urinary tract infection and erythrocyte casts were not detected in patients with hematuria. For 81.0% of the patients with hematuria, blood transfusions were initiated during their 1st year of life.

DISCUSSION

The prevalence of hematuria in beta-thalassemia major is not yet fully investigated. Only in one study from Iran,⁸ the authors compared 58 patients with beta-thalassemia major and 50 patients with thalassemia intermedia and reported hematuria in 2 patients of the former group (3.4%). Surprisingly, hematuria and pyuria were more common in beta-thalassemia intermedia compared to beta-thalassemia major.⁸ On the contrary, the prevalence of hematuria in the general population has been explored by several studies. The incidence of

hematuria is reported to be 0.5% to 2% in school-age children, depending on the definition of hematuria.^{9,10} Shajari and associates studied 1601 asymptomatic school-age children in Fars province of Iran and found the incidence of hematuria to be 1%.¹¹ Vehaskari and coworkers reported an incidence of 1.1%, with considering at least 2 serial urinalyses positive for hematuria.¹⁰ The incidence of hematuria is demonstrated to be 4.3% among adult population.¹² The results of the current study showed a higher incidence of hematuria in patients with beta-thalassemia major compared to the previous reports on normal population.

Although involvement of other organs such as liver is common in patients with beta-thalassemia major, involvement of the kidney is not as common. Renal involvement may occur by 3 mechanisms: deferoxamine side effects, deposition of iron in renal tissue, and vascular thrombosis and renal infarction due to increased platelet aggregation and decreased serum level of protein S and antithrombin III.¹³ Deferoxamine-induced kidney injury is more probable, because iron deposition may result in death of cardiac involvement, before kidney failure appears.¹³ In one study of 19 patients treated with deferoxamine,¹⁴ tubular damage (by measurement of β 2-microglobulin) was observed in 13. Acute kidney failure related to deferoxamine is usually nonoliguric and reversible with discontinuation of the drug.¹⁵

Based on autopsy reports of patients with thalassemia major, the most common glomerular findings are mesangial cell proliferation, mesangial matrix expansion, and hemosiderin deposition in glomerular and tubular cells. Iron deposition may result in tubulointerstitial fibrosis and atrophy.¹⁶ Glomerular diseases may also develop; immunoglobulin A nephropathy was reported in a patient with thalassemia major.¹⁷

In one of the recent reports from Iran on 103 beta-thalassemic patients for detection of early kidney dysfunction, the prevalence of proteinuria was high, but hematuria was not looked for.¹⁸ Due to significant correlation of proteinuria and urinary N-acetyl beta-D-glucosaminidase in that study, the origin of proteinuria was considered to be tubular. In another study from Israel, kidney function was compared between 37 patients with beta-thalassemia major, 11 with beta-thalassemia intermedia, and a control group. All the thalassemic

patients had evidence of tubular damage that directly correlated with the amount of transfused iron.¹⁹ Subclinical tubular dysfunction due to iron overload in children and adults⁴ and symptomatic hyperchloremic metabolic acidosis in an adult patient secondary to deferasirox²⁰ were reported recently. Therefore, most reports focus on tubular diseases in beta-thalassemia major rather than glomerular disorders, but this demands further investigation.

The results of our study showed that the prevalence of hematuria in patients with beta-thalassemia major younger than 10 years is not much different from that in the general population. However, in older patients, the prevalence of hematuria increased. Probably, this increased risk of hematuria in older patients is due to the increased duration of blood transfusion, iron deposition, and consumption of deferoxamine in these patients, as it was reported previously for tubular damage.^{19,20}

CONCLUSIONS

We demonstrated that in patients with beta-thalassemia major, hematuria is more common in older age groups, especially in females. Furthermore, proteinuria seems to be a common accompanying finding in patients with beta-thalassemia major and hematuria. The importance of these findings and their long-term effects on patients with major beta-thalassemia should be explored by further studies. According to the results of this study, we suggest that physicians taking care of patients with beta-thalassemia major pay more attention to the early urinary findings in such patients, in order to prevent kidney failure.

CONFLICT OF INTEREST

None declared.

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Received August 2009
Revised December 2009
Accepted January 2010