Original Article

Microalbuminuria as a Predictor of Early Glomerular Injury in Children with Sickle Cell Disease

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Abstract. ***Objective :*** A cross sectional study was carried out to determine the prevalence of microalbuminuria in the pediatric patients with sickle cell disease. ***Methods :*** The study was carried out on 64 pediatric patients aged less than 14 years with documented HbSS, HbAS and HbS beta thalassemia, Microalbuminuria was estimated using single radial immuno diffusion technique. Majority of the study subjects were of HbSS type. 38.5% had symptoms for >2 years. 18.8% of the study population had significant microalbuminuria (19.2% of SS types and 18.8% of Hb AS types). ***Result :*** Microalbuminuria excretion was significantly more in patients >9 years of age as compared to young patients ($p<0.05$). Mean serum creatinine levels did not show any significant difference in the various study groups. ***Conclusion :*** Microalbuminuria estimation is a very important clinical marker of preclinical glomerular damage in patients with sickle cell disease. Its estimation would help in the early detection of such patients and prompt initiation of therapy. **[Indian J Pediatr 2003; 70 (4) : 307-309]**

Key words : *Sickle cell; Microalbumin; Glomerulus; Kidney*

Sickle cell anemia is a disorder characterized by severe chronic hemolytic disease resulting from premature disruption of brittle, poorly deformable RBC's leading to multi-organ dysfunction. Clinical and pathological data indicate that intravascular sickling occurs more readily in kidney than in any other organ. The distribution of blood flow in the kidney and the hypertonicity of the renal medulla create a situation where red blood cells containing sickle hemoglobin undergo deoxygenation in an acidic and hyperosmolar environment that causes them to sickle more easily. Distortion of regional blood flow, focal interstitial nephritis fibrosis, tubular dysfunction atrophy, and papillary necrosis result. A series of such progressive pathological events in the kidney occur early in the life of a patient with sickle cell disease and continues throughout life.[1] Proteinuria is an early manifestation of sickle cell nephropathy, but its prevalence in sickle cell anemia has not been studied extensively in the pediatric age group. The sub-clinical increase in urinary albumin is called micro-albuminuria and is a marker of pre-clinical glomerular damage.[2] Since no Indian study was available in this regard, the aim of the present study was to determine the prevalence of microalbuminuria in pediatric patients with sickle cell disease.

MATERIALS AND METHODS

A cross sectional study was conducted in the Department of Pediatrics, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha on sixty-four patients upto 14 years of age with documented HbSS, HbAS, and HbS beta thalassemia. Patients with documented acute or chronic infection, hemodynamic instability, history of use of potential nephrotoxic medication, co-morbid condition like diabetics, hypertension ,congestive heart failure and family history of renal disease were excluded.

The diagnosis of HbSS, HbAS, HbS beta thalassemia or HbSC was based on clinical features, family history and laboratory investigations. Laboratory techniques included: Sickling test, hemoglobin electrophoresis on cellulose acetate and estimation of HbF and HbA2 levels, blood urea, serum creatinine and serum uric acid. Microalbuminuria estimation was done by Single Radial Immunodiffusion and a value more than 20 microgram/min was taken as positive. Data interpretation was done using adequate statistical tools and proteinuria was correlated with other variables by Chi Square analysis.

RESULTS

76.6% of the study subjects were less than 9 years of age and only 33.3% of all patients were between 9-14 years of age. 81.3% of the patients were of HbSS type. There was no significant difference in the sex wise distribution of the patients. Out of the total patients of SS type 20/52 (38.5%) had the symptoms for more than 2 years whereas only 20% of HbAS type had the duration of symptoms for more than one year. 51.6% of patients presented with crisis and vaso-occlusive crisis (VOC) was the most frequently encountered crisis, in 29/33 (87.8%) patients. There were only 2 patients each of sequestration crisis and

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TABLE 1. Correlation between Microalbumin Excretion and Number of Hospitalizations, Hemoglobin Levels, Crisis vs Non-crisis States and Total Leucocyte Counts.

Parameter	Total		0–4 yrs		5–9 yrs		10–14 yrs	
	n	+ (%)	n	+ (%)	n	+ (%)	n	+ (%)
1. No. of hosp.	64	12 (7.7)	28	4 (14.3)	21	3 (14.3)	15	5 (33.3)
None	15	3 (20.0)	8	2 (25.0)	6	1 (16.7)	1	-
<2	18	1 (5.6)	10	-	7	-	1	1 (100.0)
≥ 2 - <4	18	4 (22.2)	7	1 (14.3)	5	1 (20.0)	6	2 (33.3)
≥ 4	13	4 (30.8)	3	1 (33.3)	3	1 (33.3)	7	2 (28.6)
2. Hb (gms)								
< 6	8	-	4	-	1	-	3	-
≥ 6 – <8	31	6 (19.4)	13	1 (7.7)	12	1 (8.3)	6	4 (66.7)
8-<10	8	5 (27.8)	6	2 (33.3)	8	2 (25.0)	4	1 (25.0)
≥ 10	07	01 (14.3)	5	1 (20.0)	-	-	2	-
3. Crisis								
None	31	6 (19.4)	18	2 (11.1)	9	1 (11.1)	4	3 (75.0)
VOC	28	6 (21.4)	9	2 (22.2)	9	2 (22.2)	10	2 (20.0)
HH	2	-	1	-	1	-	-	-
Seques.	2	-	-	-	1	-	1	-
Stroke	1	-	-	-	1	-	-	-
4. TLC								
< 5,000	-	-	-	-	-	-	-	-
≥5,000–<10000	40	6 (15.0)	19	2 (10.5)	12	1 (8.3)	9	3 (33.3)
≥10,000–<15,000	18	4 (22.4)	6	1 (16.7)	6	1 (16.7)	6	2 (33.30
≥15000	6	2 (33.3)	3	1 (33.3)	3	1 (33.3)	-	-

hyper-hemolytic crisis while none had aplastic crisis. There was no significant difference in the mean hemoglobin concentration in patients with SS, AS and S beta thalassemia type. 18.8% of the study population had significant microalbuminuria; 19.2% of SS types and 18.8% of AS type, whereas none of the patients with S beta thalassemia types had microalbuminuria positivity. 14.3% of patients less than 9 years of age had significant microalbuminuria whereas in patients more than 9 years of age it was 33.3%. There was a significantly higher microalbumin excretion in patients more than 9 years of age as compared to younger patients ($p<0.05$). Correlation between microalbumin excretion and number of hospitalizations, hemoglobin levels, crisis vs non-crisis states and total leucocyte counts in shown in Table 1. No significant effect of these conditions on microalbumin excretion was observed. The mean serum creatinine levels did not differ significantly with the age of the patients, number of hospitalizations, hemoglobin levels, crisis vs non-crisis states and total leucocyte counts

DISCUSSION

The spectrum of renal manifestations in sickle cell disease ranges from hyposthenuria, renal tubular dysfunction, hyperuricemia, gross hematuria, papillary necrosis, urinary tract infection, proteinuria, nephrotic syndrome, hypertension and chronic renal failure. Renal manifestations are one of the least investigated in the pediatric population. It has been observed that in diabetic nephropathy, microalbuminuria preceeds the onset of proteinuria and renal impairement by upto twenty years and hence can be used to predict the development of nephropathy.[3] Similarly it is known that sickle cell glomerulopathy presents after more than 10 years of the onset of the disease.[4] and microalbuminuria estimation is an important marker of preclinical glomerular damage in these patients.[2]

The prevalence of microalbuminuria in children with sickle cell disease ranges from 8% in AS type to as high as 46% in children suffering from SS type between 10-18 years of age.[5,6,2,7] The overall prevalence of microalbuminuria in our study was

18.8 %. Majority of them were SS type (83.3%). The prevalence of microalbuminuria in SS type was 19.2 % and in AS type it was 18.8 %. This was not significant and was in contrast to the observation of significantly higher microalbuminuria in children with HbSS type as compared to HbAS type.[5] Our findings could be due to our small sample size. We observed that that the prevalence of microalbuminuria in children more than 9 years of age was significantly more ($p<0.05$) than that of younger children. This compares favourably with the findings reported by other workers.[6,7] who have found the prevalence of microalbuminuria similar to adults in older children. Aoki[3] however has not observed any correlation between urinary albumin excretion and age. Episodes of pain frequency, number of hospitalizations and hemoglobin levels have not been shown to correlate with the presence of significant microalbuminuria.[2] Similar findings have also been observed by us. However, other studies[1,6] have noted a significant increase in microalbmin excretion in sickle cell patients with lower hemoglobin levels and higher leucocyte counts. We did not observe

any statistically significant correlation between increased total leucocyte count and microalbuminuria excretion, though the patients with positive microalbuminuria had a higher total leucocyte count >15,000/cu. mm in our study too as compared to those without microalbuminuria (33% vs 17.2%).

Elevated creatinine was observed in all patients with positive microalbuminuria.[7] However, in our study the mean serum creatinine levels did not show any correlation with microalbumin excretion. This could be because of the lower mean age of our patients and relatively recent onset of the disease in majority of the study subjects as compared to the study subjects of the above study.[7] Serum creatinine is a very insensitive marker of detecting renal insufficiency in patients with sickle cell anemia and it gets elevated when the disease has reached an advanced stage. Also patients of sickle cell disease have supranormal proximal tubular function leading to increased secretion of creatinine, hence serum creatinine may be misleadingly low even in patients with significant renal impairment.[8,9]

In most of the advanced cases a renal biopsy is warranted. Renal biopsy reveals focal segmental glomerulosclerosis and mesangial proliferation.[10,11] We did not perform renal biopsies on our patients due to the relatively recent onset of the disease and presence of mild proteinuria.

The backbone of prevention is to maintain an adequate hydration and prompt treatment of urinary tract infections. Chronic transfusion therapy or hydroxyurea may also slow down progression to glomerulopathy.[12]

Therapeutic options for these patients are limited. A low protein diet is helpful in reducing proteinuria and slows down progression.[12] Short term treatment with angiotensin converting enzyme inhibitors reduces proteinuria and may improve outcome.[13] End stage renal failure develops in a small percentage of patients and these cases can be managed initially conservatively and as the disease progresses they can be considered for dialysis. Strategies for the use of recombinant Human Erythropoeitin therapy (EPO) in renal impaired sickle patients are also being evolved.[14]

A nephrology evaluation may be necessary in some cases to rule out conditions such as diabetes mellitus, hypertensive nephrosclerosis, membranous nephropathy and amyloidosis all of which may mimic sickle cell glomerulopathy.[12]

Ours was a pilot study and hence the study population was small. Larger study groups are needed to find out the true prevalence of micoalbuminuria in our children with sickle cell disease. To conclude microalbuminuria estimation is an early predictor of renal injury and if left untreated can lead to progressive renal dysfunction. Hence it is imperative that a regular screening schedule for microalbuminuria or atleast 24-hour urinary protein excretion evaluation be incorporated in the assessment of children with sickle cell anemia. This would enable early detection and prompt institution of therapeutic interventions. Parents can also be taught the importance of home monitoring for protein in urine by performing the heat coagulation test and providing them with acetic acid to decrease the false positive results.

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