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A Cross - Sectional Study of Renal Profile in Pediatric Patients with Sickle Cell Disease

Dr. Dhruti Patel[1], Dr. Omprakash Shukla[2]

Resident of Pediatrics, Government Medical College of Baroda, Vadodara, Gujarat, India
Email: *drpatel0708[at]gmail.com*

Professor of pediatrics, Government Medical College of Baroda, Vadodara, Gujarat, India
Corresponding Author Email: *opshukla101[at]gmail.com*

Abstract: ***Introduction: Sickle cell disease (SCD) is the most common hemoglobinopathy worldwide. It occurs due to a mutation in the β - globin gene located on the short arm of chromosome 11. Blockages of the small blood vessels due to sickle shape RBCs cause tissue infarction and intermittent vaso - occlusion, which are responsible for acute or chronic organ damage and organ dysfunction. Renal disease is one of the most frequent complications which starts very early and progresses throughout life causing severe complications. Objective: To study the renal function status of Pediatric patients with SCD and to detect early renal abnormalities through blood investigations, urine analysis, and ultrasonography. Methodology: A cross sectional study was conducted at the Hematology clinic and Pediatric ward of SSG Hospital and Medical college, Vadodara, Gujarat for a period of one year. A total of 100 SCD patients were enrolled and detailed clinical history, laboratory investigations, and ultrasound were performed. Results: There were 68% male and 32% female with a ratio being 2.1: 1 enrolled in the study with a mean age of 8.71 ± 3.38. Mean urea was 27.68 ± 18.9, mean creatinine was 0.71 ± 0.4, mean urine PH was 6.32 ± 0.57 with specific gravity 1.01 ± 0.005.65% had abnormal FeNa values.35% had hepatomegaly, 42% had splenomegaly, 13% had both hepatosplenomegaly and 7% had reduced kidney size. On further evaluation 4% had Proteinuria, 2% had Hematuria. According to CKD - EPI classification 23% had a normal renal function, 55% had mild, 15% had moderate, 3% had severely decreased GFR, and 4% had hyperfiltration. Conclusion: According to CKD - EPI classification 23% of the enrolled patients had a normal renal function, 55% had mild, 15% had moderate, 3% had severely decreased GFR and 4% had hyperfiltration. As age increases GFR decreases, and this was statistically proved by the p - value 1.3 × 10 - [19] ANOVA test. Proteinuria and hematuria were seen in 4% and 2% respectively in enrolled patients with normal mean urea and creatinine value.***

Keywords: Sickle cell disease (SCD), CKD - EPI, GFR, HbF, hydroxyurea.

1. Introduction

Sickle cell disease is the most common hemoglobinopathy worldwide. It is estimated to be home to over 50% of the global sickle cell disease patient population in India. It is a group of genetic disorders characterized by abnormal sickle haemoglobin synthesis (Hb S), chronic haemolytic anaemia. Sickle cell hemoglobinopathy occurs due to a mutation in the β - globin gene located on the short arm of chromosome 11, where the base adenine is replaced by thymine in the coding sequence of DNA leading to the substitution of a single amino acid glutamic acid to valine at the 6th position in the B - globin chain. This results in a profound change in molecular stability and solubility of HbS. [(1)] Most of the gain in life expectancy in recent decades has been due to early treatment with antibiotics, better pain management, and especially the use of hydroxyurea. Better and aggressive treatment for sickle cell disease has prolonged life above the age of 50 years, whereas before the 1960s only 50% of sickle cell disease patients survived to age 20 years. [(2)]

Blockages of the small blood vessels due to sickle shaped RBCs cause tissue infarction and intermittent vaso - occlusion, which are responsible for acute or chronic organ damage and organ dysfunction. Common complications of sickle cell disease include acute chest syndrome, hand, and foot syndrome, stroke, dactylitis, leg ulceration, pulmonary hypertension, jaundice, aplastic crisis, splenic sequestration, priapism, renal abnormalities, and chronic organ damage. [(1)] Renal disease is one of the most frequent complications which starts very early and progresses throughout life causing severe complications. [(2)] Because the rate of oxygen consumption by the kidney is very high (a rate exceeded only by that of the heart). The kidney is especially sensitive to vaso - occlusion induced hypoxia that can result from red cell sickling and/or sickle cell adhesion. The environment of the renal medulla is characterised by acidosis, hypertonicity and hypoxia which tend to promote haemoglobin S polymerization and red cell sickling, thereby making this area of the kidney particularly vernacular for injury. [(3)] Hyposthenuria, an inability to concentrate urine maximally, is the most frequent clinically recognized renal abnormality. It becomes apparent at an early age in sickle cell disease. Renal abnormality includes haematuria, proteinuria, microalbuminuria, and tubular abnormalities such as concentrating defect, impaired potassium excretion, and acidification defect which lead to chronic kidney disease. [(4)] Among sickle cell disease patient's prevalence of glomerular hyperfiltration is high followed by renal insufficiency and renal failure. [(2)] Sickle cell nephropathies include gross haematuria, papillary necrosis, nephrotic syndrome, renal infarction, hyposthenuria, pyelonephritis, and renal medullary carcinoma. [(5)] As the sickle cell disease patient's age increases the effect of acute and chronic tissue injury may ultimately result in kidney failure and it accounts for 10% - 15% of death in those patients. [(2)]

2. Literature Survey

- To study the renal function status of Pediatric patients with sickle cell disease through detailed clinical history, laboratory investigations, urine analysis and ultrasound.

- To detect early renal abnormalities in children with sickle cell disease abnormal ultrasound finding.

3. Material and Methods

After getting permission from the institutional ethics committee for human research (IECHR - PGR) to carry out this study with children diagnosed with sickle cell disease, children, who satisfied our inclusion criteria, were enrolled after obtaining informed written consent from their parents or guardians.

This cross - sectional study was conducted at our hematology clinical and Pediatric ward, SSG Hospital, and Medical College, Vadodara, Gujarat.

All of the 100 enrolled patients went through a full medical history, blood investigations, urine analysis, and ultrasonography.
Basic patient details like name, age, sex, address, religion, major complaints were taken from parent/guardian.

Patient's history regarding blood transfusion requirement throughout life, last blood transfusion date, at which age SCD diagnosed, number of total crises a child suffered from, the crisis in the last one year, at which age hydroxyurea started, and dose of the same was included.

Clinical examination was done which included anthropometric measures like weight, height, BMI, general examination, vitals, and systemic examination, especially per abdomen. 3ml of blood was taken with aseptic precautions and sent to biochemistry laboratory to investigate urea, creatinine, serum electrolytes for renal function test and for routine urine analysis and urinary electrolytes midstream urine was taken.

Ultrasound of abdomen was done in our radiology department, SSG Hospital and Medical College, Vadodara, hepatomegaly, splenomegaly and size of kidney were recorded.

4. Results

Table 1: Epidemiological data of enrolled sickle cell disease patients

Parameter	In Percentage
Sex	
Male	68 %
Female	32 %
Age Group	
0 - 5 Year	22 %
5 - 10year	46 %
>10 Year	32 %
Mean Age	8.71 Year
Sickle Cell Diagnosed at Age	
0 - 5 Year	67 %
5 - 10 Year	27 %
>10 Year	6 %
Average blood transfusion requirement in life	
0 - 5 Year	1.9
5 - 10 Year	3.8
>10 Year	2.3

Table 2: Laboratory results of all enrolled patients

Lab Parameter	Mean	Median ± SD
Renal Function Test		
Urea (mg/dl)	22	27.68 ± 18.95
Creatinine (mg/dl)	0.65	0.71 ± 0.4
Electrolytes		
S. Sodium (mmol/L)	139	138.2 ± 4.72
S. Potassium (mmol /L)	4.3	4.39 ± 0.69
S. Chloride (mmol/L)	110	109 ± 3.83
S. Ionised Calcium (mmol/L)	1.2	1.19 ± 0.09
Urine Analysis		
Urine PH	6	6.32 ± 0.57
Specific Gravity	1.01	1.01 ± 0.005
Urinary Creatinine (mg/dl)	39.01	49.08 ± 31.29
Urinary Sodium (mEq/dl)	107	106.71 ± 50.62
Urinary Potassium (mEq/dl)	32.5	36.43 ± 24.88
GFR Values		
Male	82.6	89.09 ± 66.72
Female	71.83	70.08 ± 20.89

Table 3: Analysis results

Mean HB F Level	
On Diagnosis	16.14 %
On Assessment	17.9 %
Mean GFR value in different Age Group	
0 - 5 Year (ml/min/1.73m^2)	90.37
5 - 10 Year (ml/min/1.73m^2)	82.98
>10 Year (ml/min/1.73m^2)	78
Overall (ml/min/1.73m^2)	83.3
CKD - EPI Classification (GFR value) in percentage	
Hyper Filtration (>120)	4 %
Stage 1 (90 - 120)	23 %
Stage 2 (60 - 89)	55 %
Stage 3a (45 - 59)	13 %
Stage 3b (30 - 44)	2 %
Stage 4 (15 - 29)	2 %
Stage 5 (<15)	1 %
Fena Value (in Percentage)	
Normal (<1%)	35 %
Abnormal (>1%)	65 %
Urine Analysis (In Percentage)	
Proteinuria	4 %
Hematuria	2 %
Ultrasound Based (In Percentage)	
Hepatomegaly	35 %
Splenomegaly	42 %
Hepatosplenomegaly	13 %
Renal Size Increased	18 %
Renal Size Decreased	7 %

There were 68% male and 32% female with a ratio being 2.1: 1 enrolled in the study. Of the 100 patients, 22% were between 1 - 5 years of age, 46% were between 5 - 10 years of age and 32% were > 10 years with a mean age of 8.71 ± 3.38.

In our study mean urea was 27.68 ± 18.9, mean creatinine was 0.71 ± 0.4, mean urine PH was 6.32 ± 0.57 with specific gravity 1.01 ± 0.005 which is considered as normal.65% had abnormal FeNa values.35% had hepatomegaly, 42% had splenomegaly, 13% had both hepatosplenomegaly and 7% had reduced kidney size. On further evaluation 4% had Proteinuria, 2% had Hematuria. According to CKD - EPI

classification 23% had a normal renal function, 55% had mild, 15% had moderate, 3% had severely decreased GFR, and 4% had hyperfiltration. This indicates abnormal renal function parameters, hematuria and proteinuria in asymptomatic patients with the above ultrasound findings.

In our study the mean value of GFR in <5 year was 90.370 ml/min/1.73m^2, in 5 - 10 years of age it was 82.980 ml/min/1.73m^2 and for >10 year, it was 78.0 ml/min/1.73m^2. From the ANOVA test, we can conclude that the GFR value decreases as age increases with a significant p - value 1.3×10^{-19}. This shows that renal function is compromised with increasing age in sickle cell disease.

5. Discussion

In a study by Bhaskar V K S, Lakkakula et al [2] conducted in a research division of Sickle Cell Institute, Chhattisgarh in 2017, the mean value of urea was 16.08 and the mean value of creatinine was 0.65. These findings are matching with our study. The same study has shown the distribution of GFR with 67.9% normal renal function, 16% with hyperfiltration and the rest with oliguria.

In a study by Dr. Bibhu Pada Hota et al [6] conducted at the Institute of Medical Science and Research Burla, Odisha in 2020, the mean value of serum sodium was 135.34 ± 4.04, the mean value of potassium was 4.05 ± 0.81 and the mean value of serum ionised calcium was 0.95 ± 0.10. In the same study, it was found that 80% of patients had normal renal size, 16% had small kidney size and 4% had increased renal size. The above result matches with our study.

According to a study by Dr. Khalid Raza et al [7] conducted at DMIMS Wardha, Maharashtra in 2018, the mean value of urine ph was 4.92 ± 0.68, the mean value of sp. Gravity was 1.010 ± 0.007, the mean value of urinary sodium loss was 73.06 ± 38.42 and the mean value of urinary potassium loss was 17.34 ± 9.06.20% of patients had normal FeNa values and 80% had abnormal FeNa values. If we observe the distribution of the patients regarding Albuminuria and Hematuria then 30% of patients enrolled had significant Albuminuria, and 25% had significant Hematuria.

A study conducted by Uchenna Modestus Nnaji et al [8] in Owerri Nigeria in 2020, had shown the mean value of GFR in < 6year 161.3 ± 28.1, in 7 - 12 year 146.7 ± 32.9, 13 - 17 year 127.9 ± 19.6. These results are matching with our study. The same study has shown p - value for the age group 1 - 6 years was < 0.001, 0.023 for the 7 - 12 years age group, and 0.828 for the 13 - 18 years age group. In the same study, 16.7% of patients had hyperfiltration, 78.3% had a normal renal function and 5% had oliguria.3.4% of patients had significant Proteinuria and 6.7% had significant Hematuria. . This is matching with our study.

6. Conclusions

- This study was done in sickle cell disease patients, who are on treatment for more than 6 months. We assessed the renal function via serum urea, creatinine, electrolytes and urine analysis.
- Mean urea was 27.68 ± 18.95, and mean creatinine was 0.71 ± 0.4 which were normal in the range.
- According to the modified Schwartz formula 4% had hyperfiltration.
- From the ANOVA test, we can conclude that the GFR value decreased as age increased.
- 4% of patients had Proteinuria and 2% had Hematuria.
- 65% of the patients showed tubular dysfunction with abnormal FeNa value.
- Based on the ultrasonographic evaluation, 35% had hepatomegaly, 42% had splenomegaly, 13%had hepatosplenomegaly, and 18% had renomegaly.
- So, we recommend periodic assessment in renal profile especially serum electrolyte, urinary electrolyte, GFR estimation in all sickle cell anemia patients.

Future Scope - Periodic assessment of renal profile especially serum electrolyte, urinary electrolyte, GFR estimation in all sickle cell anemia patients helps to identify complications in asymptomatic phase. Though our study had a small sample size, and hence more studies over a longer period and including a greater number of subjects are required to validate our results.

Declarations:

Contributions - The work described in the manuscript is our own and our individual contribution to this work is significant enough to qualify authorship.

Ethics approval - Ethical approval was obtained from the Institutional Ethics Committee for Biomedical and Health Research (IECBHR) Medical College & SSG Hospital, Baroda.

Competing interests - The authors have no competing interests to declare that are related to this study.

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