The Assessment of the Prevalence of Renal Dysfunction in Sickle Cell Patients Attending to Children Hospital

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ABSTRACT: Sickle cell disease (SCD) is an autosomal recessive genetic disorder that lead to painful crisis by entrapment of deformed red blood cells in the microcirculation in particular in renal medullary vessels. Renal involvement is documented in patients with SCD. The aim of this study was to evaluate the renal dysfunction in sickle cell patients. This was a cross-sectional study conducted among all of the patients with SCD attended to Children Hospital of Bandar Abbas in 2012. Laboratory examinations consisting of complete blood count and hemoglobin electrophoresis was performed. Serum creatinine level was measured and GFR was calculated using Bedside Schwartz equation. Urinanalysis was requested to assess urine specific gravity (SG). Demographic data (age, gender) of participants were collected. Children who had nutritional or digestive disorder or other underlying disease such as diabetes mellitus, cardiac problem and pulmonary disease were excluded. Data analysis was performed using SPSS (V.19). Frequency, mean and standard deviation was interpreted. Fifty three children with SCD were enrolled in the study and the mean age of patients was 7.7 ± 4.6 years. The most common SCD subtype was Sβ+ (N= 22, P = 39.6%). Mean hemoglobin value was 8.37 ± 1.73 and mean GFR was 148.54 ± 37.53. Among the participants, 7 (13.2%) and 4 (7.5%) had microalbuminuria and proteinuria respectively. Microalbuminuria in female patients (N = 4, P = 21.1%), was more than male (N= 3, P = 8.8%). Microalbuminuria and proteinuria increased with increasing age. But, there were no significant correlation between age and microalbuminuria or proteinuria. Further studies with higher sample size are recommended.

Key words: Sickle cell, Microalbuminuria, Proteinuria

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive hereditary disorder in which, red cells are susceptible to be deformed and sickled in an oxidative stress condition (Stuart et al., 2004). In several studies, the prevalence of sickle cell mutation reported between 20 to 30% (Weil, 2010; Sebastiano et al., 2011). Entrapment of deformed red blood cells in the microcirculation leading to tissue ischemia and consequent pain crisis (Brousse et al., 2012). Acute pain or vaso-occlusive crisis (VOC) is mostly lead to hospital admission and need to aggressive pain management, mainly including intravenous hydration and using intravenous or muscular opioids (Rees et al., 2003). End organ complications of this disease are an important subject suffer the affected patients in particular children (Gladwin et al., 2008). Renal complications of SCD are documented in many studies and are a leading cause of mortality and morbidity of children with SCD. Renal medulla has low blood flow, low PH level and high osmolality, that prone this region for red cell sickling, in consequent, medullary fibrosis and papillary necrosis will be occurred. Many studies have reported that, renal glomerular and tubular dysfunction are the most common renal pathologic findings in SCD (Tejani et al., 2008). Laboratory findings of renal dysfunction in children with SCD are varied. Hyperfiltration mostly present early, before impaired laboratory findings. Microalbuminuria is an early presentation of renal dysfunction which is detected by laboratory examination. Finally, renal function and glomerular filtration rate (GFR) decrease with increasing age and leading to hyposthenuria and hyperuricemia (Epstein et al., 1997; Ataga et al., 2000; Chatterjee, 2008). Although Hematuria caused by papillary necrosis but, it is a less frequent finding of SCD (Buckalew et al., 1974). In various studies, nephritic...
syndrome and end stage renal disease are reported between 5% and 10% of patients with SCD. Furthermore, many studies demonstrated that, sickle cell crisis and its’ life threatening complications such as pulmonary hypertension and stroke are more common in patients with chronic kidney disease (CKD) (Balkaran, et al., 1992; Sutton et al., 1994). Because of renal complications of SCD and fatal associated outcomes, we aimed to evaluate laboratory findings of renal functions in children with SCD.

MATERIAL AND METHODS

This was a cross sectional study conducted among all of the patients with SCD attended to children Hospital of Bandar Abbas in 2012. This study was approved by ethic committee of Hormozgan University of Medical Sciences (HUMS). Patients were selected based on clinical symptoms, physical examination and laboratory findings consisting of complete blood count and hemoglobin electrophoresis. Children aged between 1 and 17 years, had any type of SCD (SS, SD, Sβ+, Sβ0, or hereditary persistent fetal hemoglobin (HPFH)) were enrolled in study. Serum creatinine level was measured and GFR was calculated using Bedside Schwartz equation (k × Height in cm / Creatinine in mg/dL). Urinanalysis was requested to assess urine specific gravity (SG). Microalbuminuria was described by urinary albumin between 8 and 10 mg/g creatinin in children>6yr old. Arterial blood gas (ABG) was measured to define acid-base status of blood. And SG below 1.010 considered as hypostenuria. Demographic data (age, gender) of participants were collected. Children who had nutritional or digestive disorder or other underlying disease such as diabetes mellitus, cardiac problem and pulmonary disease were excluded. Informed consent was provided by participants or their guardians.

Data analysis was performed using SPSS (V.19). Frequency, mean and standard deviation was interpreted for parametrical and no parametrical items. Independent t-test, chi square and analysis of variance (ANOVA) were used for detection any differences between variables. Cramers V &Phi was used to determine the correlation between variables. P- Value less than 0.05 was considered statistically significant.

RESULTS

Fifty three children with SCD were enrolled in the study. The mean age of patients was 7.7 ± 4.6 years. Among the participants 34 (64.2%) and 19 (35.8%) were male and female respectively. The most common SCD subtype was Sβ+ (N= 22, P = 39.6%), followed by SD (N= 14, P= 6.4%). Twelve patients (22.6%) had SS and 5 (9.4%) had Sβ0 subtype. Only 1 patient (1.9%) had HPFH subtype. Basic characteristics of patients with SCD and markers of renal function are demonstrated in table 1.

As demonstrated in table 1, the mean values for Hb, GFR, serum creatinine, Ph and SG of urine in female were higher than males. But, only SG of urine was significantly different between male and female (P = 0.04), and other markers were not significantly different between both gender.

Also, among the subjects 17 (32.07%) had hypostenuria. The mean value of Hb among SD subtype was lower than other SCD and in HPFH subtype was higher than other groups. The mean value of Hb among SD subtype was lower than other SCD and in HPFH subtype was higher than other groups. The mean value of Hb, were not statistically significant among various subtype of SCD. The details of this parameter are listed in table 2.

Table 1. Basic characteristics of patients with SCD in male and female

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD (Total)</th>
<th>Male (Mean ± SD)</th>
<th>Female (Mean ± SD)</th>
<th>P-value</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>8.37 ± 1.73</td>
<td>8.24 ± 1.64</td>
<td>8.61 ± 1.9</td>
<td>NS</td>
<td>-1.37 , 0.62</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.45 ± 0.1</td>
<td>0.44 ± 0.1</td>
<td>0.46 ± 0.1</td>
<td>NS</td>
<td>-0.08 , 0.04</td>
</tr>
<tr>
<td>GFR</td>
<td>148.54 ± 37.53</td>
<td>148 ± 39.4</td>
<td>149.3 ± 34.9</td>
<td>NS</td>
<td>-23.15 , 20.69</td>
</tr>
<tr>
<td>SG</td>
<td>1028 ± 0.04</td>
<td>1019.6 ± 0.30</td>
<td>1044.2 ± 0.56</td>
<td>0.04</td>
<td>-0.048 , -0.0005</td>
</tr>
<tr>
<td>Ph</td>
<td>7.4 ± 0.061</td>
<td>7.4 ± 0.069</td>
<td>7.4 ± 0.043</td>
<td>NS</td>
<td>-0.02 , 0.04</td>
</tr>
</tbody>
</table>

*CI: confidence interval; NS: No significant

Table 2. Descriptive indexes and comparison between various subtypes of SCD

<table>
<thead>
<tr>
<th>SCD subtype</th>
<th>Mean ± SD</th>
<th>P – value (analyzed by ANOVA)</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>8.7 ± 1.5</td>
<td>NS*</td>
<td>0.45</td>
</tr>
<tr>
<td>SD</td>
<td>7.9 ± 2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sβ+</td>
<td>8.4 ± 1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sβ0</td>
<td>8.3 ± 0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPFH</td>
<td>9.2 ± 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8.3 ± 1.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: 0.05 significance level
Among the participants, 7 (13.2%) and 4 (7.5%) had microalbuminuria and proteinuria respectively. Also, 3 patients (5.7%) had metabolic or respiratory acidosis based on the ABG. Among 22 patients with Sβ+, 5 (22.7%) had microalbuminuria, and among 14 children with SD, 2 patients (14.2%) had microalbuminuria. There was no significant association between microalbuminuria and SCD subtypes (P > 0.05).

Also, in SS subtype, 3 patients (25%) had proteinuria and among those with Sβ+, one patient (4.5%) had proteinuria. Proteinuria had no significant association with SCD subtypes (P > 0.05).

Microalbuminuria in female patients (N = 4, P = 21.1%), was more than male (N = 3, P = 8.8%). While, 3 male patients (8.8%) had proteinuria, which was higher than female patients (N = 1, P = 5.3%). However, there were no significant difference between male and female for microalbuminuria and proteinuria (P > 0.05). The mean values of creatinine, GFR and pH had significant correlation with age (P < 0.05). While, there were no significant relation between microalbuminuria, proteinuria and urine specific gravity with age. Correlation between markers of renal function and age are listed in table 3 with details.

Table 3. Matrix correlation of renal function markers, pH and age in patients with SCD.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age</th>
<th>Serum Cr</th>
<th>GFR</th>
<th>SG</th>
<th>Microalbuminuria</th>
<th>Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Cr</td>
<td>0.32*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>0.54**</td>
<td>-0.2*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SG</td>
<td>0.15</td>
<td>0.01</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>-0.12</td>
<td>-0.07</td>
<td>-0.01</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>-0.33</td>
<td>0.1</td>
<td>0.06</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Acidosis</td>
<td>0.3*</td>
<td>-0.03</td>
<td>0.2</td>
<td>0.09</td>
<td>0.3*</td>
<td>-0.07</td>
</tr>
</tbody>
</table>

*: significant at 0.05; **: significant at 0.01

**DISCUSSION**

Because of late glomerular involvement in SCD it is not seen in early stage of this disease, and renal complications may be presented at least 10 years after the onset of disease (Ferster et al., 2001). Renal manifestations of SCD are widely investigated among several populations, but these subjects are less studied in pediatric population. Some authors showed that, microalbuminuria could be started before glomerular involvement and is a diagnostic marker to predict progression of renal disease toward glomerulopathy and more important associated complications (McBurney et al., 2002). The prevalence of microalbuminuria in our study was 13.2% which is lower than findings reported (Aoki et al., 1990; Sesso et al., 1998; McKie et al., 2007; Dharnidharka et al., 1998). In mentioned studies, the mean age of participants was higher than our study. Many studies demonstrated that the prevalence of microalbuminuria in older children is higher than younger children. And this could be the cause of higher microalbuminuria in studies reported (Aoki et al., 1990; Sesso et al., 1998; Dharnidharka et al., 1998). Also, our results showed that, the majority of patients with microalbuminuria (71.4%) were sickle beta thalassemia and the rest (28.6%) were SD, and none of the patients with SS type had microalbuminuria. These findings are inconsistent with the results of Data and colleagues (Datta et al., 2003). Interestingly, previous studies reported higher prevalence of microalbuminuria among patients with SS type than other types (McBurney et al., 2002; Datta et al., 2003; Guasch et al., 2006). Our findings indicated that 75% of patients with proteinuria were SS type. This finding could justify lack of microalbuminuria among SS type, which is a precursor for proteinuria. This shows that, our study patients with SS type developed proteinuria which is the next stage after microalbuminuria. These complications are early stages of sickle cell nephropathy. Many study examined various strategies to control and prevent the progression of microalbuminuria and proteinuria (Fitzhugh et al., 2005; McKie et al., 2007) A study demonstrated, microalbuminuria and proteinuria could be decreased in 44% and 56% of patients treated with hydroxyurea and angiotensin converting enzyme inhibitor (ACEI) respectively (McKie et al., 2007). The results of our study demonstrated microalbuminuria had no significant correlation with age, serum Cr, GFR, urine SG and patients’ Hb. McBurney and colleagues reported a contradictory results with our study results. They reported that, microalbuminuria had significant correlation with increasing age and lower Hb level (McBurney et al., 2002). This result could be due to younger population we studied. Tubular dysfunction which is characterized by inability of kidney to concentrate the urine and leading to hyposthenuria. This defect mainly defined by assessment of urine specific gravity (Cochran, 1963). In addition, it is believed that, tubular and glomerular dysfunction can develop the kidney injury in SCD (Etteldorf et al., 1952). Our findings showed that 17 (32.07%) of patients had hyposthenuria, but, results indicated that, there was no significant correlation between hyposthenuria and serum Cr. Although, GFR slightly increases in early stage of SCD however, assessment of renal function is defined better by...
GFR than other markers. The results showed that, age had significant correlation with serum Cr and GFR. In addition, the mean value of GFR was about 148 ml/min/1.73m 2, this finding is higher than other results reported by Ware (Ware et al., 2010). Our study indicated, the mean age of participants was higher than subjects studied by Ware and this could be one cause of increased GFR. Also, we found that age had significant correlation with serum Cr and GFR. These results are concordant with findings by other authors (Aoki et al., 1990; Berg, 2006). In this study we evaluated the tubular and glomerular injury in patients with SCD. Our findings showed that patients with SCD are more susceptible for glomerular and tubular dysfunction in compared to healthy population evaluated in other studies (Pham et al., 2000, Johnston et al., 2004). In addition, our results showed lower glomerular and tubular injury in compared with studies conducted by Pham et al. (2000). Also, our findings demonstrated no relation between age and progression of renal dysfunction. A finding is inconsistent with other studies (Gladowin et al., 2008; Rees et al., 2010). This could be because of more prevalent subtype of SCD in Bandar Abbas, or better follow up and treatment of patients with SCD in our hospital. This study was limited by its small sample size. Also, some patients refused to cooperate in this study. Future studies with considering higher sample size and more confounding factors which are less emphasized in our study such as duration of disease, episodes of painful crisis and co-existed disease may give more interesting and conclusive results.

REFERENCES


