Kidney function, urinalysis abnormalities and correlates in equatorial Africans with sickle cell disease

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Abstract

Background. Little is known about the renal profiles of individuals with sickle cell disease (SCD) in equatorial Africa, the global epicenter of SCD. We evaluated the kidney function, urinalysis abnormalities and their correlates in a group of Cameroonians homozygous for SCD.

Methods. This was a cross-sectional study of 4-month duration involving 72 homozygous SCD patients (39 men, 54%), recruited during routine visit or vaso-occlusive crisis at the Yaoundé Central Hospital in Cameroon. Clinical and laboratory data were used to evaluate the renal and urinalysis parameters, and potential effects of SCD-related clinical and hematological variables on those parameters investigated through linear and logistic regression models.

Results. The mean serum creatinine increased with increasing age, translating into a decreasing estimated glomerular filtration rate (eGFR) with age (P < 0.001). One patient (1.4%) had an eGFR of <60 mL/min and nine others (12.5%) had 60 ≤ eGFR ≤ 90 mL/min. The eGFR was lower in women and decreased with increasing systolic blood pressure. The prevalence of proteinuria (>200 mg/g) was 93% and the main urinalysis abnormalities were leukocyturia (77.8%), albuminuria (40.3%), hematuria (13.9%) and cristalluria (9.7%). None of the predictive clinical, hematological and urinary factors studied was associated with proteinuria or albuminuria, while hematuria and leukocyturia were associated with increasing age and male gender.

Conclusions. Cameroonians homozygous for SCD present a high prevalence of proteinuria and urinalysis abnormalities, and a slight renal impairment. Age, blood pressure variables and gender seem to be the main determinants. Urinalysis abnormalities and kidney function assessment should be an active pursuit in women with SCD.

Keywords: Cameroon; equatorial Africa; renal parameters; sickle cell disease

Introduction

Sickle cell disease (SCD) is the most prevalent genetic disease worldwide. In the classical form of the disease, there is heterozygosity in the mutation that causes hemoglobin S, while in other rare forms of the disease, hemoglobin S coexists with another abnormal hemoglobin (hemoglobin C, β-thalassemia). The disease is endemic in sub-Saharan Africa where it is associated with higher morbidity and mortality, and as a consequence, almost half of children with SCD die before their fifth birthday [1].

Continuous improvement in the quality of care has allowed SCD patients to live longer. In many affluent countries, the life expectancy has increased from ~15 years in the 1970s to the present ~50 years [2]. This improved survival is also associated with increasing occurrence of multiple organ lesions secondary to long-standing disease. The kidneys are the sixth most affected organ in SCD, and chronic renal failure is one of the main causes of death in adults with SCD [3, 4]. The kidney lesions start in childhood and mainly include glomerular and tubulo-interstitial lesions [5, 6]. The glomerular lesions evolve from hyperfiltration state characterized by an increase in glomerular filtration rate and effective renal plasma flow in association with glomerular hypertrophy to the progressive focal and segmental glomerulosclerosis, then glomerular obsolescence, proteinuria and impaired renal function. Tubular lesions are characterized...
by damages in the vasa rectae system, disruption of the countercurrent exchange, impairment of urinary concentration causing hyposthenuria and polyuria, and papillary necrosis causing hematuria [4–7]. The glomerular lesions in SCD start in the early years of life with the prevalence of albuminuria correlating with increasing age and decreasing creatinine clearance [8]. Ultimately, kidney lesions in SCD progress to end-stage renal disease in 4.2–18% of the patients [4–6]. There are suggestions that SCD may already be contributing to the burden of kidney disease among Africans [9]. However, little is known about the importance and determinants of kidney disease in SCD in equatorial Africa, where the highest global prevalence of the disease occurs [10]. We undertook this study among homozygous Cameroonians with SCD to evaluate the renal function and urinalysis parameters and investigate their predictive factors, in order to inform nephroprotection efforts in the region.

Material and methods

Study setting

This was a cross-sectional study of 4-month duration from October 2009 to January 2010, conducted at the hemato-oncology service of the Yaoundé Central Hospital in Cameroon. This is the oldest and main referral service for SCD in the country (~18 million inhabitants in 2010). The staff at the time of the study included three hematologists and several qualified nurses who each oversaw the regular follow-up of ~500 SCD patients of both genders over a wide age range, giving a good representation of the national SCD population. This study was approved by the Cameroon national ethics committee.

Data collection

During the study period, we consecutively included all homozygous SCD patients seen during routine visits or vaso-occlusive crisis (VOC), who were regularly followed-up in the Service. All patients or their next of kin (for children) provided written informed consent before enrollment in the study. Routine follow-up visits occurred once every 3–4 months for each patient. Those patients in VOC were recruited 48 h after admission to the Service (to allow a resolution of pain) and diagnosis of VOC was confirmed by the attending hematologist. Each SCD patient was included during the first contact with the investigator. We excluded from the study heterozygous SCD patients, patients with any active infection, patients with conditions that can constitute a confounding factor for urinalysis or renal function such as HIV infection, viral hepatitis B or C, diabetes mellitus, joints inflammatory diseases, systemic lupus erythematosus or urinary stone. Clinical and laboratory data for each patient were recorded using a pre-designed questionnaire. Demographic data collected included age and gender. Other clinical information included anthropometric measurements, annual frequency of VOC, other complications of SCD, history of blood transfusions and renal complications, ongoing treatment and history of tobacco or alcohol abuse. Urinary and blood biological parameters including urinary dipstick and sediment, urinary protein-creatinine ratio, serum creatinine, blood urea nitrogen and full blood count were also recorded. Urine dipstick tests were performed with CombiScreen 7SL PLUS 7 test strips (Analyticon Biotechnologies AG, D-35104 Lichentenfeis, Germany). A urine sample was collected in the morning and urinalysis was performed according to guidelines [11]. Serum and urinary creatinine were measured with a kinetic modification of the Jaffé reaction using Beckman creatinine analyzer (Beckman CX systems instruments, Anaheim, CA, USA) and total urinary protein measured using pyrogallol red-molybdate complex with Teco diagnostics tests (Teco Diagnostics, Anaheim, CA, USA). All specimens were analyzed in the Yaoundé Central Hospital laboratory as done in routine practice. Secondary variables were derived from primary variables using validated formulas.

Definitions and calculations

Regular follow-up in the Service was defined in respect to the compliance with the frequency of scheduled routine visits. Patients were classified according to the annual VOC frequency into the following categories: less frequent (<5/year), frequent (5–10/year) and more frequent (>10/year). Children below 15 years of age were considered to have low height or weight when their values were less than -2 Z-score of height or weight for age. In adults, body mass index (BMI, kg/m²) was defined by the ratio weight (kg)/height × height (m²). Thin, normal and overweight were defined, respectively, as BMI < 18.5, 18.5 ≤ BMI < 25 and 25 ≤ BMI < 30. Anemia was defined by hemoglobin levels <10 g/dL; microcytosis by mean globular volume (MGV) <80 fL; hypochromia by mean corpuscular hemoglobin (MCH) <27 pg; hyperleukocytosis by white blood cell count >10 000/mm³ and thrombocytosis by platelets count >400 000/mm³. According to the quantity of blood received, patients were classified into never transfused, transfused once and polytransfused. Estimated glomerular filtration rate (eGFR, mL/min) was calculated in children using the Schwartz equation while in adults, the Cockcroft–Gault (CG) formula, the MDRD (Modification of Diet in Renal Disease) study equation (four-variable equation) and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation were used [12–15]. The average of the CG and MDRD estimates in adults was used in the main analyses. In a sensitivity analysis, the CKD-EPI estimates were also used in adult participants. The following categories of eGFR were defined: low (<90 mL/min), normal (90–140 mL/min) and high (>140 mL/min). The 24-h proteinuria was estimated using the protein/creatinine ratio and categorized as normal (<200 mg/g), non-nephrotic range (200 to <3500 mg/g) and nephrotic range (≥3500 mg/g).

Statistical analysis

Statistical analysis was performed using the SPSS® 17 software for Windows. We reported results as mean and standard deviation, median and range, minimum–maximum, and count (percentages). Difference between variables was assessed with the use of the analysis of the variance (ANOVA) or equivalents, and χ² tests or equivalents. Generalized linear regression models and binary logistic regression models were used to investigate the determinants of kidney function and urinalysis parameters, with adjustment for potential confounders. The level of significance was set at P < 0.05.
Table 1. Baseline characteristics, kidney function test and urinalysis profile by age quartiles

<table>
<thead>
<tr>
<th>Quartiles of age</th>
<th>Total</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartiles of age</td>
<td></td>
<td>90-140</td>
<td>&gt;140</td>
<td>&lt;90</td>
<td>&gt;90-140</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>72</td>
<td>9.3 (2–14)</td>
<td>17.5 (15–19)</td>
<td>21 (20–22)</td>
<td>34.7 (25–50)</td>
<td></td>
</tr>
<tr>
<td>Median age, years (min–max)</td>
<td>19.4 (2–50)</td>
<td>12.7</td>
<td>12.6</td>
<td>9.8</td>
<td>6.12</td>
<td>0.05</td>
</tr>
<tr>
<td>Sex (men:women)</td>
<td>39:33</td>
<td>12 (11)</td>
<td>16 (8)</td>
<td>168 (8)</td>
<td>167 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean weight, SD (kg)</td>
<td>47.6 (15.4)</td>
<td>27.5 (11)</td>
<td>49.9 (7.7)</td>
<td>55.1 (6.9)</td>
<td>59.6 (9.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean height, SD (cm)</td>
<td>157 (20)</td>
<td>130 (19)</td>
<td>165 (8)</td>
<td>168 (8)</td>
<td>167 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean serum creatinine, µmol/L (SD)</td>
<td>69 (21)</td>
<td>52 (11)</td>
<td>68 (19)</td>
<td>76 (25)</td>
<td>80 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean creatinine clearance, mL/min (SD)</td>
<td>0.21 (0.11)</td>
<td>0.15 (0.07)</td>
<td>0.20 (0.10)</td>
<td>0.23 (0.13)</td>
<td>0.27 (0.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean creatinine clearance MDRD, mL/min (SD)</td>
<td>103 (26)</td>
<td>NA</td>
<td>109 (32)</td>
<td>109 (20)</td>
<td>91 (20)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean creatinine clearance CG, mL/min (SD)</td>
<td>136 (48)</td>
<td>NA</td>
<td>161 (44)</td>
<td>144 (56)</td>
<td>107 (24)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean creatinine clearance (CG and MDRD), mL/min (SD)</td>
<td>125 (35)</td>
<td>137 (31)</td>
<td>140 (32)</td>
<td>124 (39)</td>
<td>98 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean blood urea nitrogen, g/L (SD)</td>
<td>0.21 (0.11)</td>
<td>0.15 (0.07)</td>
<td>0.20 (0.10)</td>
<td>0.23 (0.13)</td>
<td>0.27 (0.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean creatinine clearance (CKD-EPI), mL/min (SD)</td>
<td>130 (32)</td>
<td>137 (31)</td>
<td>146 (26)</td>
<td>128 (35)</td>
<td>110 (23)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean serum albumin, g/L (SD)</td>
<td>72 (80–7400)</td>
<td>435 (106–1125)</td>
<td>934 (80–7400)</td>
<td>577 (150–1057)</td>
<td>576 (107–1010)</td>
<td>0.91</td>
</tr>
<tr>
<td>Creatinine (g/L)</td>
<td>0.79 (0.10–2.03)</td>
<td>0.66 (0.17–1.52)</td>
<td>0.72 (0.10–1.26)</td>
<td>0.94 (0.52–1.63)</td>
<td>0.94 (0.12–2.03)</td>
<td>0.01</td>
</tr>
<tr>
<td>Proteinuria, mg/g</td>
<td>492 (104–7843)</td>
<td>830 (146–1829)</td>
<td>1194 (146–6016)</td>
<td>661 (120–1287)</td>
<td>1075 (104–7843)</td>
<td>0.86</td>
</tr>
<tr>
<td>Creatinuria, g/L</td>
<td>495 (345–696)</td>
<td>375 (300–517)</td>
<td>520 (352–819)</td>
<td>637 (388–703)</td>
<td>580 (377–819)</td>
<td>0.22</td>
</tr>
<tr>
<td>Albuminuria, mg/g</td>
<td>0.75 (0.53–1.04)</td>
<td>0.59 (0.47–0.76)</td>
<td>0.68 (0.52–0.95)</td>
<td>0.86 (0.78–1.06)</td>
<td>0.91 (0.67–1.31)</td>
<td>0.05</td>
</tr>
<tr>
<td>Urinary protein/creatinine (mg/g)</td>
<td>697 (431–1013)</td>
<td>746 (451–1346)</td>
<td>661 (435–1066)</td>
<td>696 (453–796)</td>
<td>638 (393–1077)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Results

General profile of the study population

A total of 72 participants including 39 men (54.2%) and 33 women (45.8%) were recruited. The distribution of their characteristics across quartiles of age is summarized in Table 1 and Supplementary Table S1. The proportion of men marginally decreased with increasing age (P = 0.05 for linear trend). As expected, body weight, height and history of polytransfusion increased with increasing duration of the disease (all P < 0.02 for trend). Other clinical and biological characteristics were equally distributed across quartiles of age. Patients presented a moderate microcytic hypochromic anemia with compensatory hyperleukocytosis and thrombocytosis similarly across age strata. None of the participants had a past medical history of kidney disease or alcohol or tobacco abuse. None of them were on a chronic transfusion program, antihypertensive drugs or hydroxyurea; all participants were taking folate acid. Twenty (27.8%) patients had suffered from at least one complication of SCD. These included osteitis/osteomyelitis (35%), leg ulcers (25%), coxarthrosis (15%), left ventricular hypertrophy (10%), stroke (10%) and gall bladder stone (5%).

Blood pressure, kidney function and urinalysis profile

As presented in Figure 1, systolic and diaastolic blood pressure and proteinuria were equally distributed across quartiles of age (all P > 0.35 for trend). The mean serum creatinine and blood urea nitrogen linearly increased with the duration of the disease (both P < 0.001 for linear trend; Table 1). This resulted in a linearly decreasing eGFR across increasing age quartiles based on either the CG (P = 0.04) formula, MDRD (P = 0.001) equation, their average (P < 0.001) or CKD-EPI equation (P = 0.001). Using the average of CG and MDRD formulas, one patient (1.4%) had an eGFR of <60 mL/min, 9 (12.5%) had 60 ≤ eGFR < 90 mL/min and 22 (30.5%) presented with hyperfiltration state (eGFR > 140 mL/min). Hyperfiltration state was associated with younger age, while the reduced eGFR occurred with the duration of the disease (P < 0.002 for trend).

The urinalysis abnormalities observed were leukocyturia (77.8%), bilirubinuria (69.5%), epithelial cells (43.0%), albuminuria (40.3%), hematuria (13.9%) and crystalluria (9.7%). The prevalence of proteinuria (>200 mg/g) was 93%. The distribution of the proteinuria in the study population is depicted in Figure 2. Of the urinary parameters studied, only hematuria showed an increasing trend; Table 1). This resulted in a linearly decreasing eGFR across increasing age quartiles based on either the CG (P = 0.04) formula, MDRD (P = 0.001) equation, their average (P < 0.001) or CKD-EPI equation (P = 0.001). Using the average of CG and MDRD formulas, one patient (1.4%) had an eGFR of <60 mL/min, 9 (12.5%) had 60 ≤ eGFR < 90 mL/min and 22 (30.5%) presented with hyperfiltration state (eGFR > 140 mL/min). Hyperfiltration state was associated with younger age, while the reduced eGFR occurred with the duration of the disease (P < 0.002 for trend).

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prevalence with increasing duration of the disease ($P = 0.03$; Table 1).

Determinants of kidney function and urinary abnormalities

In age- and sex-adjusted general linear regression models, eGFR was higher in men than in women by 18 mL/min (95% confidence interval: 4–33). Using the upper age quartile as a reference, eGFR increased with decreasing age. Of the candidate predictors, only increased systolic blood pressure values were correlated to reduced eGFR [Pearson’s correlation coefficient for systolic blood pressure $−0.40$ ($P = 0.003$)]. The 24-h proteinuria was unrelated with any of the candidate predictors (Table 2).

Discussion

This group of children and adults homozygous for SCD receiving routine care at one of the largest referral services for SCD in Cameroon presents a high prevalence of proteinuria and urinalysis abnormalities, with 12.5 and 1.4% having mild and moderate renal impairment, respectively (CKD Stages 2 and 3). Age, gender and systolic blood pressure were the main determinants of those abnormalities, while disease-specific parameters including indicators of disease severity and treatment were unrelated to kidney function and urinalysis abnormalities.

The renal function and urinalysis parameters of individuals with SCD in Africa have not received significant attention. Our study findings are similar to those reported elsewhere [8, 16–18]. As observed by Guasch et al. [8], none of the patients presented with either systolic or diastolic hypertension and the hematological profile was dominated by microcytic hypochromic anemia, hyperleukocytosis and thrombocytosis. The prevalence of reduced eGFR and renal failure were lower than those reported in the literature [8, 18]. Discrepancies could be explained at least in part by differences in the methods used to evaluate renal function. When using serum creatinine alone, we did not observe values outside the normal range reported elsewhere [7]. This could be explained by the high prevalence of hyperfiltration state in our sample subsequent to alterations in renal hemodynamic or by the increased tubular secretion of creatinine which can occur in up to 40% in SCD patients [5, 19].

Albuminuria was the second most frequent urinalysis abnormality and 9 in 10 patients had proteinuria. This prevalence was higher than those reported in the literature [7, 8, 16–18, 20]. This could be explained by the high prevalence of hyperfiltration state in our sample subsequent to alterations in renal hemodynamic or by the increased tubular secretion of creatinine which can occur in up to 40% in SCD patients [5, 19].

In age- and sex-adjusted logistic regression models, only male sex was associated with leukocyturia with an odds ratio of 4.50 (95% confidence interval: 1.11–18.29). None of the other candidate predictors studied were found to be associated with urinary abnormalities (Table 3).
reduce the occurrence of proteinuria [7, 8, 16, 20]. The higher prevalence of proteinuria compared with albuminuria has also been reported elsewhere and suggests the frequent tubular lesions occurring in SCD [5–8]. However, we did not investigate tubular proteinuria to further appreciate the severity or extent of tubular lesions. Our study population included children and adults, which is contrary to most reported studies that have focused either on children or adults. This study did not find an association of albuminuria or proteinuria with clinical, biological or other urinary factors tested, which is in line with the study of Aoki and Saad [16]. However, some have reported significant associations of proteinuria with increasing age, reduced GFR, higher blood pressure, anemia, microcytosis and hyper-leukocytosis [8, 20, 21].

Hematuria was the third main urinalysis abnormality with a prevalence similar to those reported elsewhere [18, 22]. Leukocyturia was the leading urinary abnormality and was associated with male sex. This could be related to the higher frequency to the tubulo-interstitial lesions or urinary tract inflammatory process [5–7].
The present study has some limitations. The small sample size precluded reliable investigation of some of the studied questions. It is possible for instance that the absence of association of some predictors with the study outcomes was just a reflection of the limited statistical power. We did not investigate tubular lesions which tend to occur earlier in SCD, persist in such patients and contribute to the burden of the disease. Lastly, we did not screen those patients with normoalbuminuria on dipstick for microalbuminuria, which may be relevant to improve nephroprotection. Our study is unique, in that it addresses the kidney function and urinalysis abnormalities in patients with SCD in equatorial Africa where the disease is highly prevalent. By conducting this study in a referral center with national coverage, our study has generated evidence that likely reflect the disease pattern in the whole country.

In conclusion, this study revealed a high prevalence of proteinuria and a slightly reduced kidney function. The occurrence of renal impairment was mainly associated with the duration of the disease and increased systolic blood pressure; however, none of the predictive clinical, hematological and urinary factors tested was associated with proteinuria. Given the high prevalence of SCD in our setting and region, it may have value to consider the disease pattern in the whole country.

Supplementary data are available online at http://ckj.oxfordjournals.org.

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Conflict of interest statement. None declared.


References


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