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Glomerular Hyperfiltration and Albuminuria in Children with Sickle Cell Anemia

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Abstract

Early manifestations of sickle nephropathy include glomerular hyperfiltration and proteinuria, typically microalbuminuria. Over time, a subset of patients develops histologic changes, decreased glomerular filtration, and ultimately renal failure. This cross-sectional study was designed to determine the rate of glomerular hyperfiltration and prevalence of albuminuria in a cross-sectional analysis of untreated children with sickle cell anemia (SCA), and to identify correlates of both complications. Measured glomerular filtration rate (GFR) by plasma clearance of 99-technetium diethylenetriaminepentaacetate was compared to GFR estimates calculated from published formulas. Eighty-five children (mean age 9.4 ± 4.8 years) were studied; 76% had glomerular hyperfiltration with mean GFR = 154 ± 37 mL/min/1.73m^2. GFR declined in teenage years and was significantly correlated with increased serum cystatin C levels and higher systolic blood pressure. Measured GFR had only modest correlations with GFR estimates (Pearson correlation coefficients ≤0.5). Albuminuria, usually microalbuminuria, occurred in 15.9% and was associated with higher diastolic blood pressure and lower white blood cell and absolute neutrophil counts. Cystatin C levels inversely reflect GFR changes and are associated with albuminuria; serial monitoring may provide a sensitive and accurate marker of nephropathy in children with SCA.

Keywords

sickle nephropathy; glomerular hyperfiltration; albuminuria

INTRODUCTION

Clinical manifestations of sickle cell nephropathy begin early in life with glomerular hyperfiltration, hyposthenuria, and distal renal tubular acidosis, and then develop over time into albuminuria with occasional hematuria. The development of focal segmental glomerulosclerosis or membranoproliferative glomerulonephritis, hyperfiltration, albuminuria and iron deposition may contribute to diminished glomerular filtration and result in end stage renal disease that affects many young adults with sickle cell anemia (SCA). [1,2] The pathophysiology of sickle nephropathy is not well defined in its early stages, but is postulated to result from enhanced sickling in the hyperosmolar, hypoxic environment of the renal medulla with decreased blood flow, ischemia, microinfarction and papillary necrosis.[3]

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An elevated glomerular filtration rate (GFR) is one of the earliest manifestations of sickle nephropathy, and has been observed in children with SCA as young as 12 months of age with an age-dependent increase until the second decade of life.[4,5] Over time, some children with elevated GFR will develop albuminuria, but there have been only a few reports studying predictors of this complication. [4,6,7,8,9] Direct measurement of GFR by nuclear medicine techniques or 24-hour urine collection is invasive and cumbersome, so creatinine-based formulas are commonly used in clinical practice to estimate GFR. [10,11] More recently cystatin C, a small non-glycosylated basic protein whose serum concentration depends mostly on GFR, is increasingly used for this purpose. [12,13]

The aims of this cross-sectional study were (1) to determine the rate of glomerular hyperfiltration measured quantitatively by plasma clearance of injected 99-technetium diethylenetriaminepentaacetate (^{99m}Tc-DTPA); and (2) to determine the prevalence of albuminuria in a large cohort of untreated children with SCA. Other aims were to compare measured GFR values to estimates based on serum creatinine and cystatin C, and to identify correlates of hyperfiltration and albuminuria in this patient cohort.

METHODS

The Hydroxyurea Study of Long-Term Effects is a prospective observational study (HUSTLE, NCT00305175) with the goal of describing the long-term cellular, molecular, and clinical effects of hydroxyurea therapy in SCA. Enrollment in this study is offered to all children with SCA who fulfill clinical or laboratory criteria for treatment with hydroxyurea.[14] For this analysis, only the children not previously treated with hydroxyurea were included. All of the children were in their usual state of health at the time of enrollment. Prior to treatment initiation, vital signs and growth parameters such as weight and height were recorded. Blood pressure (BP) measurements were performed with the child sitting down using an oscillometric device, with an appropriate cuff size based on the child's size. Laboratory evaluations included complete blood count with white blood cell (WBC) differential, reticulocyte count, serum chemistries, serum cystatin C, quantitative urine albumin and direct GFR measurement by ^{99m}Tc-DTPA plasma clearance.

Laboratory analyses

A quantitative ^{99m}Tc-DTPA clearance study was performed on each subject at study initiation. After establishment of intravenous access, blood and urine samples were collected to perform the above mentioned laboratory studies. Next, 2mCi/m^2 (total dose: 1-4mCi) of ^{99m}Tc-DTPA were administered intravenously and plasma samples were collected at 1, 2 and 4 hours after injection using the same iv site. [15] After these specimens were analyzed, a plasma DTPA clearance curve was calculated and the quantitative GFR value was derived. Hyperfiltration was defined as GFR >1SD above the normal mean for age. In addition to direct GFR measurement, the GFR was also estimated using the following published equations:

(1) Schwartz standard formula, GFR = (height × 0.55) / serum creatinine; [10]

(2) Modified Schwartz formula, GFR = 39.1 [height (m) /serum creatinine (mg/dl)]$^{0.516}$ × [1.8/cystatin C (mg/L)]$^{0.294}$[30/BUN mg/dl)]$^{0.169}$[1.099]^{male}[height(m)/1.4]$^{0.188}$;[11]

(3) Cystatin C formula 1, GFR = −4.32 + (80.35 / cystatin C); [12] and

(4) Cystatin C formula 2, GFR = anti log {1.962 + [1.123*log (1/cystatin C)]}.[13]

Serum creatinine and cystatin C measurements were performed using the same technique at a single institution. Serum creatinine was determined by a 4-step enzymatic method (Roche Diagnostics, Indianapolis, IN) using creatininase, creatinase, sarcosine oxidase and

peroxidase to form a colored quinone imine which is measured spectrophotometrically. Serum cystatin C was quantified by a turbidimetric method (Roche Diagnostics, Indianapolis, IN) using latex particles which are coated with anti-cystatin C. Urine albumin and creatinine measurements were performed from a random single sample using a turbidimetric method at Quest Diagnostics Laboratories (San Juan Capistrano, CA). Albuminuria was defined as >30 mcg albumin/gm creatinine.

Statistical Analyses

Correlations between continuous variables were measured using the Pearson correlation coefficient and multiple variable models were constructed using linear regression. Group medians were compared with the Wilcoxon-Mann-Whitney test. Means are reported as mean ± standard deviation. This is an observational study, offering enrollment to all eligible patients treated at a single institution during the time frame of the study and no sample size calculations were made.

RESULTS

Baseline data and GFR values

Eighty-five children with SCA (56 males) were enrolled in the study before starting hydroxyurea treatment with mean age 9.5 ± 4.8 years (range 1-18 years). Seventy-seven children had HbSS and 8 had HbSB°thalassemia. The criteria for commencing treatment with hydroxyurea included recurrent vaso-occlusive painful events, acute chest syndrome, chronic hypoxemia, consistently low hemoglobin and/or high LDH level, low fetal hemoglobin or parental request. [14] None of the children were on chronic transfusion therapy or were receiving anti-hypertensive treatment. All children were normotensive based on published ranges for children with sickle cell disease[16] with mean systolic and diastolic blood pressure measurements of 108 ± 11 and 62 ± 10 mmHg, respectively. Mean serum creatinine was low at 0.3 ± 0.1 mg/dL (range 0.1-0.6 mg/dL) and serum cystatin C was within the laboratory's normal range at 0.77 ± 0.14 mg/L (range 0.57-1.25 mg/L). Mean ^{99m}Tc-DTPA GFR values were elevated at 154 ± 37 mL/min/1.73m^2 (median: 153, range: 77-308, normal for age 104 ± 20 mL/min/1.73m^2) and 76% of the children had measured GFR >1SD above the normal mean for age.[17] Measured ^{99m}Tc-DTPA GFR values were lower for patients >16 years old compared to those under 16 (133 ± 31, range: 91-176 versus 156 ± 37, range: 77-308 mL/min/1.73m^2, p = 0.0672, Figure 1).

GFR Correlations

Correlations between the measured GFR values and four GFR estimates were all statistically significant, but the strength of the associations were not as high as originally published.[10-13] Within our cohort, the best correlation was with the modified Schwartz formula (r = 0.51, p < 0.0001, Figure 2). For the other formulas, the r-values ranged from 0.34-0.40.

Measured GFR values had a significant inverse association with serum cystatin C levels (r = −0.40, p = 0.0002, Figure 3). GFR had positive correlations with both systolic and diastolic blood pressure (r = 0.28, p=0.009 and r = 0.22, p= 0.05, respectively). After adjusting for age, gender, and height, systolic blood pressure remained significantly associated with GFR (p= 0.0273) but diastolic blood pressure was no longer significant (p=0.06).

Urine albumin results

A total of 82 patients had quantitative urine albumin measurements: 13 had albuminuria for a total of 15.9%, consistent with the 15-28% prevalence previously reported for children with SCA.[6,7,8,9,18,19] Median ^{99m}Tc-DTPA GFR values were higher in patients with albuminuria, as compared to those without (164 versus 151 mL/min/1.73m^2, P = 0.22),

although this difference did not reach statistical significance. Conversely, median cystatin C values were lower in patients with albuminuria, compared to those without (0.68 mg/L versus 0.74 mg/L, p = 0.07). Patients with albuminuria had significantly higher diastolic blood pressure (67 versus 60 mmHg, p = 0.02), lower WBC (13.7 $\times 10^9$/L versus 8.6 $\times 10^9$/L, p = 0.005) and absolute neutrophil counts (ANC) (6.4 $\times 10^9$/L versus 4.5 $\times 10^9$/L, p = 0.009). Those with albuminuria also had lower Hb level (7.8 ± 1.1 versus 8.2 ± 1.1 gm/dL) and lower LDH (584 versus 660 units/L), however these differences were not statistically significant.

DISCUSSION

Our data document that a large proportion of children with SCA have glomerular hyperfiltration, even very early in life. The GFR seems to decline after 16 years of age. These lower GFR results in the second decade of life likely reflect worsening renal filtrative function, even though all of the measured GFR values were still in the normal range or slightly elevated. Since serial measurements of GFR using radionuclide scans are not practical, accurate estimates or biomarkers of GFR would be clinically useful to follow these changes in renal function over time, and potentially to predict declining renal status.

In this study, we used plasma clearance of ^{99m}Tc-DTPA to measure GFR since ^{99m}Tc-DTPA clearance has an excellent correlation with inulin clerance, which is traditionally considered to be “the gold standard” of GFR measurement. [20,21] In addition, ^{99m}Tc-DTPA clearance has been used in several other studies to measure GFR in SCA.[22,23] GFR measured by plasma clearance of ^{99m}Tc-DTPA did not correlate well with calculated GFR values, with r-values ranging from 0.34-0.51. This apparent discordance between GFR measurements and estimates is probably due to the fact that these formulas were derived primarily using data from patients with normal or decreased renal filtration. In the setting of glomerular hyperfiltration such as in SCA, GFR estimates should be used with caution and new equations should be derived. The correlations with creatinine-based formulas may be low secondary to that fact that creatinine is also secreted to a greater extent in sickle cell patients; in contrast, cystatin C is not and therefore represents a more accurate measure of GFR as evidenced by the stronger correlations with DTPA clearance.[24] As illustrated in Figure 3, even at hyperfiltration rates the serum cystatin C levels were inversely correlated with GFR values.

In a previous study of children with SCA, mean serum cystatin C levels were found to be significantly different among children with proteinuria (1.25 mg/L), microalbuminuria (0.84 mg/L) and without microalbuminuria (0.78 mg/L).[25] In addition, mean estimated GFR based on serum cystatin C was abnormal in the proteinuric group (63 mL/min/1.73m^2) as opposed to 94 mL/min/1.73m^2 in the group with microalbuminuria and 103 mL/min/1.73m^2 in the normal group. For these same cohorts, the average creatinine clearance measured by 24-hour urine collection was 133, 144 and 163 mL/min/1.73m^2, respectively. Our results extend these previous findings and suggest that cystatin C may be a useful marker for serial monitoring of renal filtration in children with SCA, and may predict declining renal status.

The observed statistical correlations of GFR with higher systolic and diastolic blood pressure measurements support a previously published report where relative systemic hypertension (120-139/70-89 mmHg) was associated with renal dysfunction in adults with SCA. [26] Becton et al have also shown that children with MA were more likely to have abnormal blood pressure.[9] Whether these results have therapeutic implications is unknown, although ACE inhibitors have been used successfully to treat elevated blood pressure and reduce protein loss among patients with SCA. [27,28,29]

In our study, similar to a previous study by Alvarez et al, [7] renal protein loss began early in life, during hyperfiltration and before the onset of GFR decline. Microalbuminuria has also been associated with older age and lower hemoglobin values[6,8,9,18,30] as well as higher leukocyte count[4] and elevated LDH. [19] In our cohort, older age, lower hemoglobin concentration and higher LDH did not reach statistical significance for renal protein loss, while lower WBC and ANC were significant associations. The previous study which showed a correlation with higher leukocyte count did not actually measure albuminuria, but rather defined proteinuria as ≥ 1+ protein detected by urinary dipstick. In another study of adults with sickle cell disease, white cell count did not correlate with the development of albuminuria.[31] In general, WBC is elevated in SCA and a relatively higher WBC reflects inflammation, and is a predictor of more severe disease and early mortality.[2,32] However, early renal damage may not reflect tissue inflammation and may be the reason why we did not find a significant correlation with elevated WBC and albuminuria.

One potential limitation of our study is the cross sectional design. We continue to collect prospective data on this cohort of children after they start treatment with hydroxyurea, so future analyses will allow analysis with serial measurements. In addition, these children with SCA fulfilled clinical/laboratory criteria that made them eligible for treatment with hydroxyurea, so represent a cohort with severe clinical disease, and not necessarily representative of all children and adolescents with SCA. Blood pressure was measured by oscillometric method rather than auscultation. Another limitation is the method of calculation for DTPA clearance; a well-established one-compartment model with a correction factor has been used instead of a two-compartment model. One final limitation was that urine albumin measurements were performed on single, spot urine specimens rather than timed collections. Despite these limitations, however, these data represent a cross sectional analysis of renal function in a large cohort of young patients with SCA, and provide insights into the relationships among glomerular hyperfiltration, microalbuminuria, and cystatin C in this patient population.

These data suggest serum cystatin C is a sensitive and accurate early marker of renal dysfunction in children with SCA, similar to reports in acute renal injury, liver or stem cell transplantation, cardiac surgery, and diabetes.[33-39] Cystatin C levels are lower in young children reflecting the elevated GFR and remain low during adolescence; only in later teenage years do cystatin C levels rise as GFR declines and renal dysfunction progresses. For individual patients, increasing cystatin C measurements may indicate declining GFR and worsening renal function, even if conventional GFR estimates remain within the normal range. Serial monitoring with cystatin C, as recently demonstrated for patients with diabetic hyperfiltration, may lead to early identification of patients with SCA at risk of nephropathy, potentially at an early stage when interventions may be more effective.[39]

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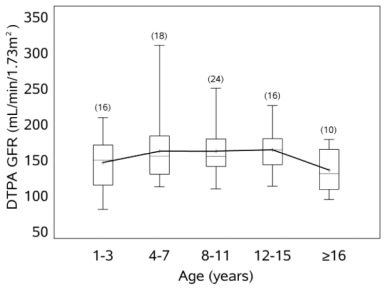

Figure 1.

Glomerular filtration rate by age group. The measured DTPA GFR values are illustrated in standard box and whisker plots. Boxplots display the minimum, first quartile, median, third quartile, and maximum for each age group. Group means are marked with a cross and connected with a line. The number of patients in each age group is shown in parentheses.

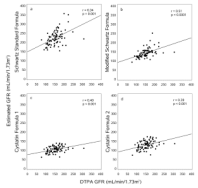

Figure 2.
Measured DTPA GFR values versus estimated GFR using the original Schwartz formula (a), modified Schwartz formula (b),and two cystatin C based formulas GFR = −4.32 + (80.35 / cystatin C) (c), and GFR = anti log {1.962 + [1.123*log (1/cystatin C)]} (d).

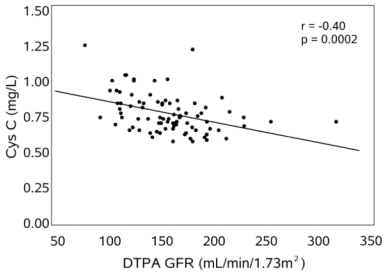

Figure 3.
Measured DTPA GFR values versus serum cystatin C levels (r = −0.40, p = 0.0002).