Full Length Research Paper

Persistent proteinuria among sickle cell anaemia children in steady state in Ilorin, Nigeria

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Sickle cell disease (SCD), the commonest single gene disorder amongst Nigerian children, may present as sickle cell nephropathy (SCN). SCN is detectable by persistent proteinuria, a "nephrotoxin" that contributes to progression of SCN to end stage renal disease. Unfortunately, screening for persistent proteinuria is an uncommon practice among Nigerian children with SCD, even when reduction of proteinuria is a proven renoprotective therapy. Dipstick urinalysis was done to detect persistent proteinuria (proteinuria of trace and above, on first contact and a month on follow-up in the same subject) among consecutive steady state sickle cell anaemia (haemoglobin SS confirmed using cellulose acetate paper electrophoresis) children attending sickle cell clinic at the University of Ilorin Teaching Hospital between October, 2004 and July, 2005. Subjects with persistent proteinuria were also assessed for estimated glomerular filtration rate (eGFR) using the method described by Schwartz et al. A total of 75 children aged between 1 to 17 years, comprising 35 males and 40 females, were studied. Proteinuria was found in 6 (8%) subjects (5 males, 1 female) and in 5 (6.7%) subjects (3 males, 2 females) on first contact and one month on follow-up, respectively. Persistent proteinuria was only seen in 3 (4%) male subjects (older than 10 years age) whose eGFR was not impaired. Although proteinuria occurred more commonly among male subjects than females on first contact and at follow-up, this observation was not statistically significant (p = 0.175 at first contact, p = 0.224 at follow-up). Proteinuria also occurred more among subjects older than 10 years of age at both contacts, this association was also not significant (p = 0. 071 on first contact, p value = 0.10 at follow-up). Although, a low prevalence of persistent proteinuria was found among the sickle cell anaemia children studied, its screening should become a routine to identify children who will benefit from antiproteinuric treatment.

Key words: Persistent proteinuria, steady state sickle cell anaemia, children, Ilorin, Nigeria.

INTRODUCTION

Nigeria, by virtue of her population, is the most sickle cell disease (SCD) endemic country in the world, with over 40 million people (24% of its population) being a carrier of the Haemoglobin "S" gene; and the prevalence of sickle cell anaemia (SCA) being about 20 per 1000 births and about 150,000 children born each year with the disorder

(Sickle Cell Foundation, 2016). The cause of the SCD is the substitution of valine for glutamic acid at the sixth position of the β-goblin chain of the haemoglobin (Nath and Hebbel, 2015). The immediate consequence of the mu-tation is that deoxygenated haemoglobin S polymerizes and distorts the shape of the erythrocytes (Manwani and Frenette, 2013). Sickled haemoglobin also causes oxidative damage of the erythrocyte membrane, cellular dehydration, abnormal phospholipid asymmetry and increased adherence to endothelial cells (Francis and Johnson, 1991; Hebbel, 1991). The net result of these alterations is a shortened erythrocyte life span from chronic haemolysis and episodic microvascular occlusion that cause tissue ischaemia and acute and chronic dysfunction of virtually all the organs of the body including the kidney (Oral and George , 1993; Alhwiesh, 2014). The kidney's microvasculature is particularly vulnerable because of absence of collateral circulation and the characteristic sickling promoting features of the renal medulla including the low oxygen tension, acidosis and hypertonicity (Alhwiesh, 2014).

A variety of renal structural and functional abnormalities have been consistently found in patients with SCD in what is now termed sickle cell nephropathy (SCN) (Allon, 1990; Lopez and Andres, 2011; Alhwiesh, 2014). The structural changes in the cortex and the medulla include vascular dilatation and engorgement of glomerular capillaries with sickled erythrocytes, glomerular hypertrophy, glomerular sclerosis, mesangial proliferation as well as focal scarring and papillary necrosis in the medulla (Allon, 1990; Lopez and Andres, 2011; Alhwiesh, 2014). The functional alterations manifest clini-cally as proteinuria with or without nephrotic syndrome, haematuria, impaired urinary concentration, increased susceptibility to urinary tract infection, incomplete distal tubular acidosis, impaired potassium excretion abilities, increased glomerular filtration rate and renal plasma flow in young patients but with progressive decline of these values after the third decades of life (Allon, 1990; Lopez and Andres, 2011; Alhwiesh, 2014).

In Nigeria, studies on SCN among sickle cell anaemia (SCA) children in the steady state had involved measure-ment of proteinuria/microalbuminuria and the glomerular filtration rate (GFR). Persistent proteinuria of 7% was reported in Port Harcourt, Southern Nigeria, by Ugwu and Eke using the dipstick urinalysis (Ugwu and Eke, 2002). Solarin et al. (2014) in Lagos, Southern Nigeria reported microalbuminuria prevalence rates of 11.3 and 38.8% using the albumin creatinine ratio (ACR) and the micral test, respectively. In addition, using the micral method, a respective microalbuminuria of 42.7 and 20.3% was reported by Yaguo-Ide et al. (2010) in Port-Harcourt, Southern Nigeria and Abhulimhen-Iyoha et al. (2009) in Benin-city, Southern Nigeria.

Although the dipstick proteinuria is not sensitive for the detection and quantitation of microalbuminuria; the persistent proteinuria detectable by it is a signal indicator of a glomerular lesion (Kallen et al., 2013). Persistent proteinuria is nephrotoxic and it plays a central role in the progression of glomerular lesions to later stages of chronic kidney disease (Kallen et al., 2013). Furthermore, Oyinade (1973) in Lagos Western Nigeria demonstrated a significantly higher mean GFR in SCA children compared to age-matched controls without SCA. Other Nigerian researchers (Aikhionbare et al., 1988; Okoro and Onwuameze, 1991; Olowu et al., 2002) did not find a significant difference in the mean GFR between the two groups.

Whereas, infection is the leading cause of death among children with sickle cell anaemia, deaths from chronic renal failure takes prominence after the first three de-cades of life (Platt et al., 1994). This becomes important because with improvement of knowledge of medical management of the disease and in better living standards, a longer survival is expected among these children and hence the risk of death from renal failure may become more frequently encountered (Anigilaje and Adedoyin, 2013).

This study determined the prevalence rates of persistent proteinuria and its association with age and gender among SCA children attending the sickle cell clinic at the University of Ilorin Teaching Hospital, Ilorin, Nigeria. SCA subjects with persistent proteinuria were also assessed for estimated GFR to determine the extent of renal impairments.

MATERIALS AND METHODS

Study area

The study took place at the Sickle cell clinic of the Department of Paediatrics and Child Health of the University of Ilorin Teaching Hospital (UITH), Ilorin, Kwara State, Northern Nigeria. The UITH provides tertiary health care services to the people in Ilorin metropolis and the adjoining cities and communities. UITH also serves as a referral Centre for the surrounding States of Kogi, Niger, Ekiti, Oyo and Osun.

Consent and ethical approval

Permission to embark on the study was gotten from the Research and Ethics Committee of the University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria. Written informed consent was obtained from the parents/legal care providers of the children that constitute the study population. The study design complied with the Helsinki declaration. The study's objectives were explained to the parents/legal care providers of the study population and it was emphasized that the information obtained from the study would be treated with the utmost confidentiality. It was also underscored that anyone was at liberty to decline participation and that declination to participate would not affect the care and treatment of the children.

Study population

Subjects were SCA children (haemoglobin, HbSS, determined by electrophoresis using cellulose acetate paper) in the steady state.

Table 1. Age-group and gender distribution of the subjects.

Age group (years)	Male	Female	Total (%)
< 5	10	12	22 (29.3)
6-10	11	15	26(34.7)
11-15	10	8	18(24.0)
≥ 16	4	5	9(12.0)
Total	**35**	**40**	**75(100)**

We had earlier reported the burden of haematuria in the same cohort of subjects (Anigilaje and Adedoyin, 2013). Included in the study were SCA children between 9 months and 18 years of age. They were assumed to be in the steady state when they satisfied the following criteria (Ojuawo et al., 1994): (i) No fever at presentation and for 4 weeks preceding clinical attendance, (ii) No complaints of skeletal and/or abdominal pain at presentation and within the 4 weeks preceding the investigation, (iii) Not on any medication apart from routine folic acid and proguanil, (iv) Otherwise well and going about their routine activities. Exclusion criteria included subjects with: (i) Symptoms and signs suggestive of urinary tract infections, (ii) At least 4 weeks history of exposure to radio-opaque dye and some drugs that decrease the reactivity of dipstick reagents including nitrofurantoin, cephalexin, cephalothin, captopril and tetracycline (Davis and Avner, 2004; Bayer Diagnostics, 2004), (iii) Menstruation or vaginal/penile discharge (Davis and Avner, 2004; Bayer Diagnostics, 2004), (iv) Fever (Davis and Avner, 2004; Bayer Diagnostics, 2004), (v) Involvement in competitive sport/exercise in the previous 24 h (Davis and Avner, 2004; Bayer Diagnostics, 2004).

Sample size

A minimum sample size of 42 for the subjects was calculated using the Leslie Kish's method (Kish, 1965) at a standard normal deviate of 1.96, assuming 2.8% target population (Adewuyi and Akintunde, 1990) and tolerating 5% sampling error. We limited response rate to 80%, giving a rounded figure of 53. Although a total of 80 SCA children met the inclusion criteria, a total of 75 were evaluated at follow-up (five subjects were lost to follow-up). These 75 subjects comprised 35 males and 40 females with a male to female ratio 1:1.1. Their age range was between 1 to 17 years, with a mean age of 8.9 ± 4.5 years. The age group and gender distribution of the subjects were as shown in Table 1

Study design

A prospective longitudinal study in which consecutive SCA patients (HbSS) who came for routine follow-up clinic over 10 months between October, 2004 to July, 2005 were recruited. In order to define a persistent proteinuria on dipstick urinalysis findings, two clinical contacts were required, the second contact being a month after the first one.

Specimen collection

All enrolled subjects were provided with a properly labeled universal bottle for the collection of early morning urine. Subjects were instructed on how to collect early morning mid-stream urine depending on the age. The care givers collected for subjects who could not collect on their own. Urine samples so brought were

accepted when subjects still satisfied the inclusion criteria. The lead investigator was available as early as 7.00 a.m. to receive urine specimens. Early morning urine is expected to be concentrated and therefore most suitable for biochemical analyses (Clinical and Laboratory Standards Institute, 2001). When tests could not be performed within the first hour of urine collection, urine was stored in the refrigerator (at 4°C) and tested within two hours of storage in the refrigerator. Urine refrigerated was kept at room temperature for 15 min before tests were performed. Dipstick urinalysis was done using Multistix 10SG by Bayer Diagnostic (Bayer Diagnostics, 2004). All instructions regarding the storage, handling of reagent strip and the performance of the dipstick urinalysis were observed as stipulated by the manufacturer. The grades of findings on colour chart and their corresponding quantitative values were as follows; negative, trace (15 mg/dl), 1+ (30 mg/dl), 2+ (100 mg/dl), 3+ (300 mg/dl) and 4+ (2000 md/dl).

Glomerular filtration rate measurement

GFR was estimated for all subjects with persistent findings on dipstick urinalysis. The GFR in ml/min/1.73 m^2 was estimated using the formula described by Schwartz et al. (1987).

$$GFR = \frac{KL}{Sc}$$

Where K = constant of proportionality
= 0.55 for children and adolescent girls (13-21 years of age)
= 0.70 for adolescent boys (13-21 years of age).
L = body height in cm.
Scr = Serum creatinine in mg/dl.

About 4 ml of blood was collected into a plain ethylene diamine tetra-acetic acid EDTA bottle for Scr estimation using the Jaffe's method on Corning colorimeter reading at 520 nanometers (Newman and Prize, 1999). The height was measured by a standard method to the last 0.1 cm. Hyperfiltration; eGFR value more than 140 ml/min/1.73m^2 (Aloni et al., 2014)

Statistical analysis

Data analysis was done with the Epi-info Software package (version 6.04) and SPSS 11.1. Subjects were grouped into increasing age-groups of four (1 to 5, 6 to 10, 11 to 15, and ≥ 16 years). Descriptive statistics were tabulated as numbers and percentages for categorical variables. The prevalence of persistent proteinuria was calculated. Chi square (×2) test was adopted to test for association between the age groups and gender and proteinuria. P value of < 0.05 was regarded as significant.

RESULTS

Table 2 shows the proteinuria on dipstick urinalysis for subjects on first contact and at follow-up. Proteinuria was found in 6 (8%) subjects (5 males, 1 female) and in 5 (6.7%) subjects (3 males, 2 females) on first contact and at follow-up, respectively. Persistent proteinuria was only seen in 3 (4%) male subjects. Although proteinuria occurred more commonly among male subjects than females on first contact and at follow-up, this observation

Table 2. Proteinuria for subjects on first contact and at follow-up.

Age groups (years)	Subjects without proteinuria		Subjects with proteinuria		Subjects with Persistent proteinuria	
	Male	Female	Male	Female	Male	Female
1-5	9 (10)	11 (12)	2 (0)	1 (0)	0	0
6-10	11 (11)	15 (14)	0 (0)	0 (0)	0	0
11-15	8 (8)	8 (8)	2 (2)	0 (0)	2	0
≥16	3 (3)	4 (4)	1 (1)	0 (2)	1	0
Total	31 (32)	38 (38)	5 (3)	1 (2)	3	0
Prevalence rates in %	41.3 (42.7)	50.7 (50.7)	6.7 (4)	1.3 (2.6)	4	0

Table 3. The estimated glomerular filtration (eGFR) rates of the three male subjects with persistent proteinuria.

Serial number	Age	eGFR (ml/min/1.72 m^2)
7	14	114
12	15	107
55	17	140

was not statistically significant (p = 0.175 at first contact, p = 0.224 at follow-up). Proteinuria also occurred more among subjects older than 10 years of age at both contacts, this association was also not significant (p = 0.071 on first contact, p value = 0.10 at follow-up). Figures in parenthesis were findings at follow-up. Relationship between gender and proteinuria on first contact (X^2= 4.963, df = 3, p value = 0.175) and at follow-up; (x^2 = 4.376, df = 3, p value = 0.224). Relationship between age and proteinuria on first contact (X^2 = 15.814, df = 9, p value = 0.071) and at follow-up (X^2 = 21.479, df = 9, p value = 0.10).

Table 3 depicts the estimated glomerular filtration rates of the three subjects with persistent proteinuria. None of the 3 male subjects with persistent proteinuria had impaired GFR as their eGFRs were all above 60 ml/min/1.73 m^2.

DISCUSSION

The prevalence of proteinuria of 8.0% noticed on the first contact among our subjects dropped off to 6.7% on follow-up, one month after, but persisted in 3 male subjects with a persistent proteinuria prevalence rate of 4%. This finding differed from that of Aikhionbare et al. who did not find persistent proteinuria among the 22 SCA subjects studied (Aikhionbare et al., 1988). However, the prevalence of persistent proteinuria of 4.0% in this study was higher than the persistent proteinuria of 6.2% reported both, in the USA and in Congo by Wigfall et al. (2000) and Aloni et al. (2014), respectively among SCA children, even though the subjects of Aloni et al. (2014) appear to be younger (2 to 13 years old).

Furthermore, the prevalence of persistent proteinuria in this study was lower than 12.3% reported by Morgan among 407 Jamaican SCA patients and the 7% reported by Ugwu and Eke among 72 SCA children in Port Harcourt, Nigeria (Morgan, 1982; Ugwu and Eke, 2002). While the discrepancy in this study and that of Morgan may be due to the difference in age composition of the two studies (1 to 17 years in this study and 1 to 70 years in Morgan's); that of Ugwu and Eke may not be easily explained as they also studied children in a relatively similar age groups with ours (16 months to 16 years).

In general, inter-observer differences in the reading of dipstick urinalysis cannot be totally ignored and may also be responsible for the different rates of proteinuria observed in our study and those of Wigfall et al. (2000), Aloni et al. (2014), Morgan (1982) and Ugwu and Eke (2002). We are very careful in comparing our study with those of other Nigerian researchers (Solarin et al., 2014; Yaguo-Ide et al., 2010; Abhulimhen-Iyoha et al., 2009) as these researchers measured microalbuminuria in Nigerian children with SCA in contrast to dipstick proteinuria measured in this study. Although, the dipstick urinalysis mainly detects albumin among the various proteins in urine and it is sensitive to albumin concentrations as low as 15 mg per deciliter; it is not sufficiently sensitive for detecting albumin in the range of microalbuminuria (that is, albumin excretion of 30 to 300 mg per day) (Kallen et al., 2013).

Although proteinuria occurred more commonly among male subjects than females on first contact and at follow-up, this observation was not statistically significant. The pathophysiology of proteinuria among SCA patients is not gender dependent and the observed gender related differences in this study may therefore be due to a chance

chance occurrence as more male subjects were seen during the study period.

Proteinuria was found more among subjects older than 10 years in this study, this trend was not statistical significant. Furthermore, the three subjects with persistent proteinuria were also older than 13 years of age. Nicholson had earlier reported that proteinuria did not occur in SCA children below the age of 10 years but affected older age group (Nicholson, 1977). Wigfall et al also noted that the prevalence of proteinuria in SCA patients increased with increasing age, ranging from 0.0% in children 1 to 6 years to 12.0% in older teenagers (Wigfall et al., 2000). Medullary and cortical infarctions resulting from incessant vaso-occlusive crises gets cumulatively worsened with age and this may probably explain the reason why proteinuria is commoner in older SCA patients (Allon, 1990; Yaguo-Ide, 2010; Lopez and Andres, 2011; Alhwiesh, 2014).

Luckily, the eGFR in all the three subjects was relatively normal, perhaps in keeping with the fact that the proteinuria is yet to damage the glomeruli in these subjects. However, hyperfiltration of eGFR greater than 140 ml/min/1.73 m^2 cannot be rule out as one of the subjects was having eGFR of 140 ml/min/1.73 m^2. Recently, an intrinsic glomerulopathy related to endothelin (ET)-1 production and signals and nitric acid synthesis have been reported and may also explain the proteinuria seen in SCD patients (Tharaux, 2011; Lopez and Andres, 2011; Aloni et al., 2014).

Proteinuria in SCN has been attributed to glomerular capillary hypertension. This concept of glomerular hypertension induced proteinuria is supported by the reduction in protein excretion that is observed with the administration of angiotensin-converting enzyme inhibitors (Sharpe and Thein, 2014; Scheinman, 2009). Proteinuria may also accompany the membranoproliferative lesions of SCN (Nath and Hebbel, 2015). The membranoproliferative lesion has been thought to result from an autologous immune-complex nephritis, although the nature of antigens triggering the immune response remains speculative and even when known, such immune reactants are often considered non-specific (Nath and Hebbel, 2015).

Conclusion

The study reveals that the prevalence of persistent haematuria is low in this cohort of SCA children in steady state. Although not statistically significant, proteinuria is commoner among boys than girls who are often older than age of 10 years. Although microalbuminuria detects renal impairment much earlier than the dipstick urinalysis, SCA children can still benefit from screening with dipstick urinalysis, especially when the proteinuria is found to be persistent. Progression of SCN to end stage renal disease can be achieved through the prevention of incessant crises and the control of proteinuria with angiotensin-1-converting enzyme inhibitors (Anigilaje and Adedoyin, 2013). The three children with persistent proteinuria in this study also benefited from lisinopril on follow-up at the sickle cell clinic.

Conflict of interest

The authors have not declared any conflict of interest.

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