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Establishing sickle cell diagnostics and characterizing a paediatric sickle cell disease cohort in Malawi

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Sickle cell disease (SCD) is the most prevalent genetic disease in sub-Saharan Africa and an estimated 240,000 children are born with SCD each year (Piel *et al.*, 2013). Similar to Africa as a whole, Malawi has a substantial SCD burden but scarce resources for diagnosis and treatment (Brabin *et al.*, 2004; Piel *et al.*, 2013). Neither neonatal screening nor standardized methods for SCD diagnosis currently exist, as haemoglobin electrophoresis and alternative diagnostic methods are typically absent; consequently, all patients with suspected SCD in Malawi have been diagnosed using clinical criteria alone in recent years. To begin addressing the diagnostics and care gap, we implemented haemoglobin electrophoresis testing in the capital city, Lilongwe, in January 2015. We report baseline clinical and laboratory characteristics of children with confirmed SCD. These data provide a foundation for future studies to understand the natural history of SCD in Malawi and develop intervention strategies appropriate for the setting to improve outcomes.

Study subjects were recruited from a paediatric chronic care clinic at Kamuzu Central Hospital (KCH) between January and May 2015. Haemoglobin electrophoresis was completed using whole blood preserved in EDTA-coated tubes, haemolysed in a saponin-

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Author Contributions:

JBH, NSK, KIA, AP and SG designed the study. JBH, GC, PK, RK, YM and PM collected the data. JBH, YF and SG analysed the data. JBH and SG wrote the first draft while NSK, KIA and YF contributed to subsequent drafts.

Conflicts of Interest:

We declare no conflicts of interest.

based reagent and analysed using a Quickgel Chamber system and Titan Plus power source (both from Helena Laboratories, Beaumont, TX). Complete blood counts were performed on an A^{C}•T 5diff CP Hematology Analyzer (Beckman Coulter, Atlanta GA), blood serum chemistries using a Cobas c311 analyser (Roche Diagnostics, Basel, Switzerland) and urine dipsticks (Bayer Multistix 10 SG, Bayer AG, Leverkusen, Germany). The University of North Caolina-Chapel Hill institutional review board and Malawi National Health Science Review Committee approved the study. Written informed consent was obtained from parents of all enrolled children. Children aged 7-17 years also provided informed assent prior to study participation.

A total of 137 patients with clinically suspected SCD were enrolled between January and May 2015. Of those enrolled, 117 patients were confirmed to have HbSS, two were HbAS, 12 were HbAA and the diagnosis was uncertain in six patients. Of 125 children who were under long-term care for SCD prior to enrolment, 107 (86%) were confirmed to have HbSS. No patients were double heterozygous for HbS and HbC or β-thalassaemia. Baseline clinical parameters and historical complications are listed in Table I. A high proportion of the total population (79%) was receiving malaria prophylaxis with sulfadoxine/pyrimethamine (SP) at study enrolment. Prior malaria was reported by 39% of patients, and tended to be higher in the 0-5 years age group compared to the group aged over 5 years (46% vs. 31%, p=0.03). Seventy-two per cent reported prior anaemia, followed by joint pain (56%), jaundice (52%) and acute pain episodes (50%). Most patients reported a history of blood transfusions (74%). Nocturnal enuresis was reported by 21% and no patients reported haematuria. Baseline laboratory parameters are found in Table II. Urinalysis revealed the presence of blood in 26% of patients, although microscopy was not performed to assess the presence of red blood cells. Proteinuria was found in 7% of patients.

In our experience, local clinicians were generally accurate in identifying children with SCD on clinical grounds alone. However, many children without SCD were being treated as such, and children with non-classical presentations and younger ages are probably not receiving appropriate diagnosis and treatment in settings where suitable diagnostic methods are lacking (Grosse *et al.*, 2011). Children with confirmed SCD in Lilongwe had substantial morbidity, and commonly reported histories of anaemia, jaundice, joint pain and pain episodes. Nearly 10% of our population reported a history of stroke, similar to other African SCD cohorts in which prevalence of prior stroke is 7-13% in adolescent SCD populations (Njamnshi *et al.*, 2006).

Seventy-four per cent of SCD patients had a history of blood transfusion despite an erratic local blood supply in Malawi, with most having been transfused within the last year. A history of repeated blood transfusion was independently associated with mortality among children with SCD in Kenya (Makani *et al.*, 2009). Defining optimal approaches to transfusion therapy for children with SCD in sub-Saharan Africa is important, where limited supply may impair wide-scale applicability of chronic transfusion to prevent severe complications, such as stroke (Adams *et al.*, 1998). Malaria is also a significant cause of morbidity and mortality for SCD patients in endemic regions (McAuley *et al.*, 2010). Approximately 80% of children with SCD in our cohort were receiving malaria prophylaxis. Despite high rates of prophylaxis, 39% of patients reported a history of malaria. A history of

malaria was significantly more common in our cohort among children aged <5 years, and earlier SCD diagnosis using haemoglobin electrophoresis may allow earlier initiation of chemoprophylaxis at younger ages. Patients exhibited moderate anaemia and leucocytosis, with elevated bilirubin and lactate dehydrogenase (LDH) levels, as expected with the haemolytic process in SCD. In addition to reflecting active haemolysis, LDH is associated with microalbuminuria, a biomarker for renal damage in paediatric SCD patients (Gurkan *et al.*, 2010). Renal disease in SCD is a significant cause of morbidity and mortality in the United States and a recent study in West Africa suggests that renal involvement is under-recognized in sub-Saharan Africa (Ranque *et al.*, 2014). In our population, 26% of patients had haematuria by urine dipstick assessment, possibly reflecting haemoglobinuria, which is associated with chronic kidney disease in SCD (Saraf *et al.*, 2014). Twenty-one per cent of the population also reported nocturnal enuresis, a symptom of hyposthenuria secondary to a medullary concentrating defect. Additionally, 7% of the cohort had proteinuria, a particularly high prevalence in this young patient cohort. Taken together, these findings suggest that a significant proportion of children with SCD in Malawi exhibit renal involvement, and may be at risk for worsening nephropathy and end-stage renal disease as they grow older.

In conclusion, haemoglobin electrophoresis implementation in Lilongwe provides a foundation for detailed cross-sectional description of paediatric SCD patients in Malawi. Children had substantial clinical and laboratory evidence of SCD-related morbidity. Earlier diagnosis can substantially improve care for this population by facilitating earlier therapeutic interventions, as well as providing a basis for research to better understand SCD-related morbidity in sub-Saharan Africa. These baseline data can inform management strategies to improve outcomes and increase life expectancy among children with SCD in Malawi.

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Table I

Baseline clinical parameters and historical complications for ambulatory children with HbSS in Lilongwe.

	All (n=117)	Male (n= 62)	Female (n=55)	p value
Age years, median (IQR)	7.3 (2.7-10.4)	5.3 (2.3-9.4)	8.9 (4.2-11.9)	**0.004**
Height cm, median (IQR, n)	115 (88-131, 60)	111 (89-128, 36)	119.5 (93-140, 24)	0.21
Weight kg, median (IQR, n)	19 (13-27, 108)	16.5 (12-23.6, 58)	21 (14-30, 50)	**0.01**
Blood Pressure Systolic mmHg , median (IQR, n)	103 (98-110, 83)	101 (94-108, 43)	103 (99-110, 40)	0.37
Blood Pressure Diastolic mmHg, median (IQR, n)	60 (55-65, 83)	58 (53-65, 43)	61 (56-68, 40)	0.13
Heart Rate BPM, median (IQR, n)	104 (91-118, 114)	105 (94-123, 61)	104 (88-112, 53)	0.15
O_2 Saturation % (room air), median (IQR, n)	93 (88-97, 108)	91 (85-96, 59)	95 (91-98, 49)	**0.004**
% Hypoxaemic (SPO_2 < 90%), n (%)	36 (30.7)	26 (41.9)	10 (18.2)	**0.005**
Body Temperature, °C, median (IQR, n)	37 (36.7-37.4, 91)	37 (36.7-37, 46)	37 (36.4-37.2, 45)	0.22
Positive History of:				
Malaria, n (%)	45 (38.5)	22	23	0.34
0-5 years, n (%)	25 (46.3)	-	-	**0.03**
6-18 years, n (%)	20 (31.7)	-	-	
Pneumonia, n (%)	29 (24.8)	10 (16.1)	19 (34.5)	**0.02**
TB, n (%)	7 (6.0)	4 (6.5)	3 (5.5)	0.82
HIV, n (%)	0	0	0	-
Anaemia, n (%)	84 (71.8)	49 (79.0)	35 (63.6)	0.06
Pallor, n (%)	16 (13.7)	7 (11.3)	9 (16.4)	0.43
Jaundice, n (%)	61 (52.1)	33 (53.2)	28 (50.9)	0.82
Received blood transfusion, n (%)	87 (74.4)	47 (75.8)	40 (72.7)	0.47
Median units received (range)	1.5 (1-10)	1 (1-8)	2 (1-10)	0.73
Days since last transfusion, median (IQR)	316 (133-1144)	240 (111-410)	577 (180-1784)	**0.03**
Pain episodes, n (%)	58 (49.6)	27 (43.5)	31 (56.4)	0.16
Joint pain, n (%)	66 (56.4)	33 (53.2)	33 (60.0)	0.34
Dactylitis, n (%)	41 (35.0)	19 (30.6)	22 (40.0)	0.29
Leg ulcers, n (%)	5 (4.3)	5 (8.1)	0	**0.03**
Stroke, n (%)	10 (8.5)	5 (8.1)	5 (9.1)	0.84
Nocturnal Enuresis, n (%)	24 (20.5)	12 (19.4)	12 (21.8)	0.74
Haematuria, n (%)	0	0	0	-

IQR, interquartile range; BPM, beats/min; SPO_2, peripheral capillary oxygen saturation; TB, tuberculosis; HIV, human immunodeficiency virus

Table II

Baseline laboratory parameters for ambulatory children with HbSS in Lilongwe.

Complete Blood Count	**All (n=113)**	**Males (n=58)**	**Females (n=46)**	**Unit**	**p value**
White blood cell count, median (IQR)	16 (12.2-19.2)	16.5 (12.8-19.6)	15.9 (11.9-18.9)	$\times 10^9$/l	0.18
Hb, mean (IQR)	73 (69-79)	72 (66-78)	75 (70-79)	g/l	0.12
Haematocrit, mean (IQR)	22.6 (21-24.6)	22.2 (20-24.6)	22.9 (21.3-24.7)	%	0.14
Mean Corpuscular Volume, mean (IQR)	88.2 (83-94)	88 (83-94)	88.3 (82.5-94)	fl	0.88
Platelet Count	450 (351-586)	435.5 (364.5-565)	485 (323-588)	$\times 10^9$/l	0.97
Absolute Neutrophil Count	5.39 (4.3-6.7)	5.4 (4.5-6.5)	5.4 (4.0-6.7)	$\times 10^9$/l	0.98
Lymphocyte Count	7.9 (5.9-10.8)	8.6 (6.1-11.2)	6.3 (5.7-10.2)	$\times 10^9$/l	**0.03**

Serum Chemistries	**All (n=115)**	**Males (n=62)**	**Females (n=53)**		
Creatinine, median (IQR)	26.5 (17.6-26.5)	26.5 (17.6-26.5)	26.5 (17.6-35.6)	µmol/l	0.15
Total Bilirubin, median (IQR)	29.1 (18.8-44.5)	29.1 (18.8-42.8)	29.1 (17.1-49.6)	µmol/l	0.97
Direct Bilirubin, median (IQR)	10.3 (6.8-13.7)	10.3 (6.8-13.7)	10.3 (6.8-15.4)	µmol/l	0.98
Lactate Dehydrogenase, median (IQR)	658 (527-773)	664 (544-773)	634 (517-772)	iu/l	0.54

Urine Dipstick	**All (n=100)**	**Males (n=51)**	**Females (n=49)**		
Glucose, n (%)	3 (3)	0	3 (6.1)		0.06
Bilirubin, n (%)	12 (12)	7 (13.7)	5 (10.2)		0.69
Specific gravity, median (IQR)		1.015 (1.01-1.02)	1.015 (1.01-1.015)		0.82
Blood, n (%)	26 (26)	10 (19.5)	16 (32.7)		0.09
pH, median (IQR)		6 (5.5-6.3)	5.5 (5.5-6)		0.86
Protein, n(%)	7 (7)	3 (5.9)	4 (8.2)		0.57
Urobilinogen, median (IQR)		3.4 (3.4-17.1)	3.4 (3.4-17.1)	µmol/l	0.64
Positive nirtrite, n(%)	7 (7)	5 (9.8)	2 (4.1)		0.31
Leucocytes, n(%)	19 (19)	0	19 (38.8)		**<0.001**