Diagnosis patterns of sickle cell disease in Ghana: a secondary analysis using cohort data

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Abstract

Background:

Despite having the highest prevalence of sickle cell disease (SCD), Sub-Saharan Africa lacks a robust screening program. We sought to capture the diagnosis patterns of SCD, particularly age and mechanism at SCD and age of first pain crisis, in Accra, Ghana.

Methods

We administered a survey to parents of offspring with SCD between 2009–2013 in Accra as a part of a larger cohort study and analyzed a subset of the data to determine diagnosis patterns. Univariate analyses were performed on diagnostic patterns; bivariate analyses were conducted to determine if patterns differ by offspring's age, or their disease severity. Pearson's chi-squared were calculated.

Results

Data was collected on 354 unique participants from parents. 44% were diagnosed with SCD by age four; 46% had experienced a pain crisis by the same age. 66% were diagnosed during pain crisis, either in acute (49%) or primary care (17%) settings. Younger (< 18 years) offspring were diagnosed with SCD at an earlier age (74% by four years old); in the adult (> = 18 years) group, 30% were diagnosed by four years (p < 0.001). Few were diagnosed via newborn screen. Half with severe disease were diagnosed by age four, compared to 31% with mild disease (p = 0.009).

Conclusions

These findings reflect a reliance on diagnosis in acute settings, and a relative underutilization of systematic screening programs. By understanding current patterns, opportunities remain to more effectively detect and treat SCD in this high prevalence population.

Background

Sickle cell disease (SCD) is a collection of genetic disorders that affect the human red blood cell (1). Microscopically, red blood cells for those with SCD have a "sickled" appearance, and those with SCD are prone to hemolytic anemia and vasoocclusive events resulting in pain, acute chest syndrome, stroke, and other complications (2). There are many different forms of SCD, with hemoglobin-SS (HbSS), an inheritance of two abnormal S type hemoglobin, being the most common type. Life expectancy for this most common form of the disease has improved with advances in care (3–5), but morbidity and mortality still remain disturbing internationally.

The highest prevalence of SCD is in sub-Saharan Africa (2, 6), where it is a major contributor to mortality for children less than five years of age (7). Identifying SCD in the newborn period improves health outcomes; however, no country in sub-Saharan Africa has a universal newborn screening program for hemoglobinopathies. Despite the presence of a federal approach, several countries have demonstrated success with implementing local and regional testing (8–10). The lack of infrastructure to identify and manage sickle cell disease throughout sub-Saharan Africa is thought to be in part due to co-located communicable disease, such as HIV and malaria, and a corresponding large morbidity and mortality from them, relatively (11).

Early diagnosis of SCD is critical. Ghana has made progress in testing newborns, where 2% of newborns are estimated to have SCD (12). Piloting of newborn screening for SCD started in the mid-1990s, and has showed success with 170,000 newborns having been screened to date, with more than 80% maintaining follow up. However, there is currently no universal screening program for SCD in Ghana.

We sought to better understand, given the lack of comprehensive testing for SCD in Ghana, the diagnostic patterns for SCD in Accra, Ghana, and to determine whether diagnostic pattern differed by child age or disease severity. This analysis was a part of a larger, longitudinal cohort study completed at Korle Bu Teaching Hospital (KBTH). We hypothesized that our findings would reflect a reliance of SCD diagnosis in the acute setting, and that those with more severe disease would be diagnosed earlier in life.

Methods

We analyzed data that were a part of a longitudinal sibling cohort study conducted between 2009–2015 at KBTH. Parents were eligible for participation if they had at least two children with SCD, with laboratory confirmation. The children attended the pediatric health center at KBTH. The goal of the larger cohort study was to determine the SCD phenotype within the Ghanaian SCD population. The larger cohort study was approved by the Institutional Review Board (IRB) at the University of Michigan Medical School and the Noguchi Memorial Institute for Medical Research IRB at the University of Ghana. SCD diagnostic information, including method of diagnosis and age at diagnosis for children with SCD, was captured from parent participants, and analyzed for this work. This sub-analysis was approved as exempt by the IRB at Children's National Hospital.

Parents completed a voluntary, in-person questionnaire about their child's SCD, available in English and translated into their native dialect (Ga, Twi, etc.) if needed. The parent's child is considered the "participant" here, and categorized as either an adult or child based on age. We defined an adult participant as a person 18 years of age or older at the time of the survey administration. Of note, some of these parents were able to reflect on the health of their children with SCD who, at the time of the survey, were adults themselves. Univariate analyses were performed on diagnostic patterns; bivariate analyses were conducted to determine if diagnosis patterns differ by the participant's age (child or adult at the time of parent's survey) or disease severity. Severe disease was defined as HbSS or sickle beta thalassemia-zero and mild disease was defined as hemoglobin SC or sickle beta thalassemia-plus disease. Pearson's

chi-squared was used to compare the frequencies between groups. Level of statistical significance was set at $p < 0.05$. Fisher's exact was used in cases where cells were present with values less than five. Quantitative analysis was conducted using STATA IC Version 15 (13).

Results

Surveys from a total of 354 unique participants, completed by their parents, were collected. There were minimal missing data, which is reflected in Tables 1-3. The median age for participants was 23 years (Table 1). Sixty-eight percent of the participants were adults greater than or equal to 18 years. Half (54%) were female. Nearly all were of Ghanaian descent. Two-thirds had HbSS disease. Forty-four percent were diagnosed with SCD by age four, and a similar number had experienced a pain crisis by the same age (46%). Two-thirds were diagnosed during pain crisis, either in the hospital or emergency department setting (49%) or at the pediatrician's office (17%).

We next analyzed responses based on participant age at the time of their parent's completion of the survey (<18 or >= 18 years) to determine whether diagnostic patterns differed based on whether or not the parent was reporting on an adult child (Table 2). Younger participants were diagnosed with SCD significantly earlier (74% by four years old); in the adult group, 30% were diagnosed by age four ($p<0.001$). Few participants were diagnosed via screening in the newborn period (6% overall, 8% of adults, 1% of children). Younger children were less likely to be diagnosed via a medical evaluation for a pain crisis (55%) in comparison to adult children (70%), and more likely to be tested and diagnosed because another child in the family had SCD (19%, compared to 2% in the adult group) ($p<0.001$). Interestingly, the adult group reflected an older age for first pain crisis compared to the younger group (32% with first pain crisis by age 4 in the adult group compared to 69% with first pain crisis by age 4 in the younger age group) ($p<0.001$).

We further analyzed the data to understand whether disease severity was associated with diagnostic patterns. Two-thirds of all participants had severe disease and one-third had mild disease (Table 3). Half with severe disease were diagnosed with SCD by age four, compared to 31% with mild disease ($p=0.004$). There were not significant differences in diagnosis mechanism based on disease severity ($p=0.132$). As expected, those with severe disease were diagnosed earlier in life compared to those with mild disease (50% of those with severe disease diagnosed by four years of age compared to 36% of those with mild disease diagnosed by the same age) ($p=0.047$).

Discussion

The SCD diagnosis patterns in this group reflect a reliance on diagnosis in acute settings. Two-thirds of our participants in this cohort were diagnosed with sickle cell disease during a pain crisis. More than half of our respondents had not been diagnosed with SCD by age four based on parent report. The analysis of diagnosis mechanism by age (< 18 or > = 18 years old) suggests a shift to earlier diagnosis. There was a

relative underutilization of systematic screening programs, as compared to Western nations where broad based, comprehensive screening programs exist.

A reliance on diagnosis in an acute setting is problematic for a myriad of reasons. Patients miss out on essential preventative care when they are not identified early in life and encounter otherwise preventable complications. For example, people with SCD are more likely to develop serious, invasive disease from bacterial organisms such as *Streptococcus pneumoniae*. Prior to vaccinations efforts, these bacterial infections were the cause of death for most pediatric SCD deaths (14). After the introduction of the first pneumococcal conjugate vaccine (PCV7), invasive pneumococcal disease decreased by 93% in children under 5 years old (15). Prophylactic treatment with penicillin soon after SCD identification has shown similarly successful results and positively impacted morbidity and mortality in pediatrics SCD (16). Early identification of SCD in the newborn period results in successful enrollment in vaccination programs and prophylactic care for SCD patients. It may also empower parents and caregivers with relevant information on SCD complications. A 2010 study found that, when infected with malaria, HbSS patients were more likely to experience severe anemia and death (17). Appropriate, evidence-based anticipatory guidance to prevent SCD complications is achievable with early SCD recognition. Further, the significant morbidity and mortality related to SCD, particularly in the population that this study queries, places a strain on the health care system that could be partially mitigated with early identification of disease (18). Universal newborn screening for SCD certainly would be a step towards connecting at risk children to vital care early in life, relieve health care expenditures, and better distribute the health care workforce (19).

There are certainly limitations in this work that must be addressed and should be considered in concert with our findings. First, there is likely selection bias present. Those that live in remote or rural locations may not have been reflected in the results, given that this work was executed in partnership with an academic medical center. In addition, parents in this study were asked to reflect on the health of their children retrospectively. Given the wide age range of the participants (some still in childhood and some who had reached adulthood by the time of their parent's completion of the study), there is likely significant recall bias present, especially for the adult participants. Parents may have struggled to remember the diagnosis mechanisms or age of first pain crisis for their older children. Prospective cohort studies will be of utmost importance to better understand SCD diagnosis patterns in international populations, and to develop creative, multidisciplinary strategies to prevent disease complications and enhance quality of life (20).

In conclusion, this work adds significantly to the existing literature. Our findings support a dependence on SCD diagnosis in the setting of pain crisis in this cohort in Accra, Ghana, as opposed to systematic diagnosis in the pre-symptomatic newborn period. Late diagnosis, in toddlerhood or school-age childhood, places SCD patients at risk for disease complications and early death. Stakeholders would do well to consider a multidisciplinary approach to complication prevention. In this population with relative high prevalence of SCD, there remain immense opportunities for early disease identification, and a comprehensive approach in the newborn period, including diagnosis, connection to subspecialty care, and enrollment in preventive campaigns (21).

Declarations

Ethics Approval and Consent to Participate: The larger cohort study was approved as human subjects research by the Institutional Review Board (IRB) at the University of Michigan Medical School and the Noguchi Memorial Institute for Medical Research IRB at the University of Ghana. All procedures performed in studies involving human participants were in accordance with the ethical standards of the IRB at both University of Michigan and Noguchi Memorial Institute for Medical Research and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This sub-analysis was approved as exempt by the IRB at Children's National Hospital. Data was anonymized and irreversibly deidentified to protect individual participant privacy. Informed consent was obtained from all individual participants included in the study.

Consent for Publication: not applicable

Availability of Data and Materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests: All authors indicate that they do not have competing interests.

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Tables

Table 1: Participant Demographics	
Variable	**All (n = 354)**
Age (years)	
Median (IQR)	23 (13 – 32)
Adults	235 (67.7%)
Children (<18 years)	112 (32.3%)
Missing age=7	
Sex	
Male	164 (46.5%)
Female	189 (53.5%)
Missing sex=1	
Patient Genotype	
Severe Disease	
Hemoglobin-SS	230 (65.5%)
Sickle Beta Thalassemia-zero	5 (1.4%)
Mild Disease	
Hemoglobin-SC	111 (31.6%)
Sickle Beta Thalassemia-plus	3 (0.9%)
Other	2 (0.6%)
Missing genotype=3	
Age of Sickle Cell Diagnosis	
0-6 months old	39 (11%)
7-11 months old	19 (5.4%)
1-2 years old	56 (15.8%)
3-4 years old	43 (12.2%)
5-10 years old	101 (28.5%)
11-14 years old	41 (11.6%)
15+ years old	55 (15.5%)
No missing data	
Mechanism Sickle Cell Diagnosis	
“Blood test…”	
For pain crisis	
At the hospital/ER	169 (49.3%)
At the pediatrician’s office	57 (16.6%)

Because child in family had SCD	26 (7.6%)
At birth (newborn screen)	19 (5.5%)
For another illness (not pain crisis)	55 (16%)
Other	17 (5%)
Missing diagnosis mechanism=11	

ER: emergency room

SCD: sickle cell disease

Table 2: Participant Diagnosis Patterns, by Age		
Variable	**Adults (n=235)**	**Children <18 years (n=112)**
Age of Sickle Cell Diagnosis (p<0.001)		
0-6 months old	27 (11.1%)	12 (10.7%)
7-11 months old	4 (1.7%)	15 (13.4%)
1-2 years old	20 (8.5%)	34 (30.4%)
3-4 years old	20 (8.5%)	22 (19.6%)
5-10 years old	78 (33.2%)	22 (19.6%)
11-14 years old	34 (14.5%)	6 (5.4%)
15+ years old	53 (22.6%)	1 (0.9%)
No missing data		
Mechanism Sickle Cell Diagnosis (p<0.001)		
"Blood test…"		
For pain crisis		
At the hospital/ER	116 (51.3%)	48 (43.2%)
At the pediatrician's office	43 (19%)	13 (11.7%)
Because child in family had SCD	5 (2.2%)	21 (18.9%)
At birth (newborn screen)	18 (8%)	1 (0.9%)
For another illness (not pain crisis)	32 (14.2%)	23 (20.7%)
Other	12 (5.3%)	5 (4.5%)
Missing diagnosis mechanism=11		
Age of First Pain Crisis (p<0.001)		
0-6 months old	16 (8.7%)	2 (2%)
7-11 months old	1 (0.5%)	2 (2%)
1-2 years old	30 (16.2%)	46 (45.1%)
3-4 years old	12 (6.5%)	20 (19.6%)
5-10 years old	69 (37.3%)	28 (27.5%)
11-14 years old	21 (11.3%)	3 (3%)
15+ years old	36 (19.5%)	1 (1%)
Missing first pain crisis=64		

ER: emergency room

SCD: sickle cell disease

Fisher's exact used where individual cells <5

Table 3: Participant Diagnosis Patterns, by Disease Severity		
Variable	**Severe (n=235)**	**Mild (n=116)**
Age of Sickle Cell Diagnosis (p=0.009)		
0-6 months old	30 (12.7%)	9 (7.8%)
7-11 months old	15 (6.3%)	4 (3.5%)
1-2 years old	44 (18.6%)	12 (10.3%)
3-4 years old	31 (13.1%)	11 (9.5%)
5-10 years old	64 (27%)	37 (31.9%)
11-14 years old	27 (11.4%)	14 (12.1%)
15+ years old	26 (11%)	29 (25%)
No missing data		
Mechanism Sickle Cell Diagnosis (p=0.132)		
"Blood test…"		
For pain crisis		
At the hospital/ER		
At the pediatrician's office	105 (46.1%)	63 (55.3%)
Because child in family had SCD	43 (18.9%)	14 (12.3%)
At birth (newborn screen)	15 (6.6%)	11 (9.7%)
For another illness (not pain crisis)	15 (6.6%)	4 (3.5%)
Other	41 (18%)	14 (12.3%)
Missing diagnosis mechanism=11	9 (4%)	8 (7%)
Age of First Pain Crisis (p=0.047)		
0-6 months old	14 (7.3%)	4 (4.1%)
7-11 months old	3 (1.6%)	0 (0%)
1-2 years old	62 (32.3%)	17 (17.4%)
3-4 years old	18 (9.4%)	14 (14.3%)
5-10 years old	58 (30.2%)	39 (39.8%)
11-14 years old	16 (8.3%)	8 (8.2%)
15+ years old	21 (10.9%)	16 (16.3%)
Missing first pain crisis=64		

ER: emergency room

SCD: sickle cell disease

Fisher’s exact used where individual cells <5