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CASE REPORT

Sickle Cell Disease in Early Infancy: A Case Report

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Abstract: Sickle cell disease (SCD) refers to a group of hereditary disorders that result in faulty hemoglobin carriage by the red blood cells. This paper discusses an atypical presentation of SCD in early infancy. Despite current literature suggesting protection by fetal hemoglobin in the first few months of life, we report a diagnosis of SCD at 2 months of age with severe symptoms requiring hospitalization. It is therefore important for clinicians to raise their clinical index of suspicion of SCD in children presenting with severe anemia even though they are less than 6 months old and do not present with classic dactylitis or pain syndromes. Expansion and sustained newborn screening programs for SCD in developing countries could help clinicians and parents plan for early treatment, appropriate prophylaxis, and improved management of SCD complications.

Keywords: sickle cell disease, severe anemia, malaria, invasive pneumococcal disease, newborn screening, infancy

Introduction

Sickle cell disease (SCD) refers to a group of hereditary disorders that result in faulty hemoglobin carriage by the red blood cells (RBCs).[1] It is caused by an autosomal recessive mutation of the beta globin chain which in turn codes for abnormal hemoglobin S instead of hemoglobin A.[2] The World Health Organization estimates that 5% of the world population carries a hemoglobinopathy[3] and the global birth estimate of homozygous SCD is 112 per 100,000 live births, with Africa leading at 1,125 per 100,000 births[4] and predominance in the black and brown communities in sub-Saharan Africa.[5] The severity and clinical course of SCD may vary based on several factors, including genotype, family knowledge about the disease, and health care access. Fetal hemoglobin (HbF), made up of 2 alpha/2 gamma chains as opposed to 2 alpha/2 beta chains like adult hemoglobin, prevents RBCs from sickling under stress. As fetal hemoglobin persists up to 6 months of life, with a residual amount (<1%) going into adulthood, in regions with no newborn screening programs, children with sickle cell are usually identified beyond the age of 6 months.[6] In Africa, newborn screening programs remain limited, with only a few countries maintaining consistent newborn screening programs.[7,8] In Zambia, the newborn screening program was launched in April 2021, with screening scheduled to be conducted at three hospitals nationwide.[9]

We report a case of sickle cell disease with severe anemia in a 10-week-old male.

Case Presentation

A 10-week-old baby boy presented to Chawama First Level Hospital in Lusaka, with a history of i) coughing for 2 weeks prior to the visit, ii) sneezing, iii) refusing to breastfeed, iv) intermittent fevers, and v) general irritability and being difficult to console. His medical history revealed that he was HIV exposed (HEI) and had been on neonatal prophylaxis (Nevirapine 1.5 mL OD, Zidovudine/lamivudine 1.5 mL BD, Cotrimoxazole 2.5 mL OD) from birth and HIV DNA PCR testing done at 6 weeks was negative. The child was born at term via spontaneous vaginal delivery, had a birth weight of 3.8 kg, was exclusively breastfed, and received all age-appropriate vaccinations (BCG and OPV at births; OPV, PCV, Rota, and HepB, HiB, DPT at 6 weeks). There was no family history of sickle cell disease or positive tuberculosis contact.

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The child had previously received paracetamol and nasal saline drops at home before hospital presentation, with no improvement. Review of systems was unremarkable, in addition, there was no history of similar presentation prior to this episode.

On examination, the child was ill-looking, irritable, pale, and febrile with nasal flaring. The child's temperature was 38.8°C, weight was 5 kg, heart rate was 142 b/min, respiratory rate was 38 b/min and oxygen saturation was 97% on room air. Chest examination revealed anterior coarse crepitations bilaterally. All other systemic examinations were normal. An impression of pneumonia and severe anemia r/o malaria was made prior to investigations and the child was referred to the University Teaching Hospital for further management.

Blood investigations revealed a bicytopenia (Hemoglobin, HB 3.7 g/dL, White cell count, WCC $5.2x10^9$/L, Platelets $143x10^9$/L), red cell anomalies (sickle cells, target cells, poikilocytosis, anisocytosis, microcytosis, hypochromia, schistocytes, and slight macrocytic anemia) and raised liver function tests (bilirubin 38.7 µmol/L, AST 43.3 IU/L, protein 67.2 g/L). Blood culture showed *Staphylococcus haemolyticus* and *Streptococcus pneumoniae* with common sensitivity to levofloxacin, moxifloxacin, clindamycin, and linezolid. *Staphylococcus haemolyticus* also showed multi-drug resistance to ciprofloxacin, erythromycin, tetracycline, and co-trimoxazole (Table 1). Hemoglobin electrophoresis test results showed a HbS percentage of 90.5% and a HbF percentage of 2.9% (Table 2).

A diagnosis of Sickle cell disease with sepsis and pneumonia was made after a review of laboratory results. He received two blood transfusions with packed red blood cells (160 cc), intravenous crystalloid fluids, broad-spectrum antibiotics (cefotaxime 200 mg IV TDS, then ciprofloxacin 100 mg PO BD), and oral analgesics (paracetamol 80 mg PO

Table 1 Laboratory Results at First Admission

Infant HIV DNA PCR:	**Negative**			
Full Blood count:				
White cell count	$5.18x10^9$/L			
Red blood cells	$1.36x10^{12}$/L			
Haemoglobin	3.7 g/dL			
Haematocrit	11.9%			
MCV	87.5 fL			
MCHC	31.1 g/dL			
Platelets	$143x10^9$/L			
Differential count:				
Neutrophils	45% $1.99x10^9$/L			
Lymphocytes	50.1% $2.20x10^9$/L			
Sickling test:	Positive			
Peripheral blood smear	Red cell morphology – Sickle cells, anisocytosis, poikilocytosis, microcytosis, hypochromic, schistocytes, target cells			
White cell morphology	Normal			
Platelet morphology	Thrombocytopenia noted on film			
Blood culture				
Organism identification	*Streptococcus pneumoniae* and *Staphylococcus hemolyticus*			
Antibiotic susceptibility	STRPN	STAHA	STRPN	STAHA
Ciprofloxacin	S	R	Quinupristin/dalfopristin	S
Levofloxacin	S	I	Nitrofurantoin	S
Moxifloxacin	S	S	STRPN, *Streptococcus pneumoniae*	
Erythromycin	S	R	STAHA, *Staphylococcus* haemolyticus	
Clindamycin	S	S	[S]usceptible [R]esistant [I]ntermediate	
Linezolid	S	S		
Tetracycline	S	R		
Co-trimoxazole	R	R		
Gentamicin		S		

Table 2 Abnormal Hemoglobin Studies Hb Variants

Investigation	Observed Value
Foetal hemoglobin (HbF) Hemoglobin A0 (HbA0) Hemoglobin A2 (HbA2) Hemoglobin S (HbS)	2.9% 2% 4.6% 90.5%
Impression: Suggestive of Sickle Cell Disease (?Homozygous HbS) (?HbS-Beta Thalassemia) Method: HPLC	

TDS). The patient proceeded to recover well with the resolution of cough, fever, and HB restoration to 8.8 g/dL. He was discharged 13 days post-admission on haematinics (folic acid 5 mg daily) and malaria prophylaxis (deltaprim ¼ tab weekly).

Two months after discharge the child was readmitted with a 1 day history of fever, irritability, and excessive crying. Examination revealed an irritable child with oral thrush and severe pallor but no jaundice. Anthropometrics and vitals recorded at presentation were: Weight 5.8 kg, Temperature 37.4°C, Heart rate 165 b/min, Respiratory 56 b/min, O_2 Sat 95% on room air. All other systems were normal except the child was noted to cry whenever he was lifted. In addition to his HIV post-exposure prophylaxis medication, he was also taking folic acid 5 mg OD and deltaprim ¼ tab weekly. Laboratory results at this presentation showed severe aeamia (HB 2.8 g/dL) with leucocytosis (WCC $56.2x10^9$/L), and MCV was 93.6 FL (Table 3).

During the second admission, the child was treated for vaso-occlusive crisis (VOC) with sepsis in SCD and oral candidiasis. He received intravenous fluids, 2 units packed red blood cell transfusion (160 cc), Nystatin 200,000 iu PO QID, Benzyl penicillin 290,000 iu IV QID, Paracetamol syrup 2.5 mL PO TDS and oxygen by nasal prongs. The child was admitted for 5 days and HB at discharge was 9.2 g/dL.

The child returned to the hospital 2 weeks post-second discharge with a 3 day history of weakness and reduced activity. On examination, his pulse was 168 b/min, respiratory rate 42 b/min, temperature 37.9°C, and oxygen saturation of 86% on room air. He was conscious, in respiratory distress, and very pale. All other systems were normal. During this admission, the child's laboratory results were positive for Malaria (*P.falciparum*) on RDT, HB 2.2 g/dL, WCC $50.9x10^9$/L, and MCV 90.1 FL (Table 4). During his third admission, he was treated for Malaria with severe aaemia (hemolytic crisis) in SCD. He received 2 units of packed red blood cells (160 cc) and Artemether-Lumefantrine 1 tablet initial, then 1 tablet after 8 hours, then 1 tablet PO BD for 2

Table 3 Laboratory Results at Second Admission

Full Blood Count:	
White cell count	56.20×10^9/L
Red blood cells	$0.93x10^{12}$/L
Hemoglobin	2.8 g/dL
Hematocrit	8.7%
MCV	93.6 fL
MCHC	31.8 g/dL
Platelets	$140x10^9$/L
Differential count: Not done	

Table 4 Laboratory Results at Third Admission

Full Blood Count:	
White cell count	$34.50x10^9$/L
Red blood cells	$0.60x10^{12}$/L
Hemoglobin	2.2 g/dL
Hematocrit	6.0%
MCV	100.0 fL
MCHC	36.7 g/dL
Platelets	$200x10^9$/L
Differential count:	
Neutrophils	19.2% $9.77x10^9$/L
Peripheral blood smear	Unsuitable for testing
Reticulocyte count	Not done
RDT Malaria (p.f)	Positive

days, folic acid 5 mg PO OD, deltaprim ¼ tablet PO weekly. He was discharged on day 7 post-admission with an HB of 12.5 g/dL.

Discussion

Typically, sickle cell disease is diagnosed in infancy or before the age of 3 years with a great number presenting after the age of 6 months.[10] The age at diagnosis is lower in children with HbSS than those with HbAS according to a retrospective study concluded in 2009 with the average age of diagnosis being 2 years old (24–25 months) and this was the same for non-endemic areas.[11,12] This is in tandem with the natural history of the disease or physiology of fetal hemoglobin waning. Despite the introduction of newborn screening programs in many developed countries, children with sickle cell disease continue to be identified later than 1 year of life.[13] Similarly, in countries yet to introduce newborn screening programs, diagnosis usually coincides with onset of clinical symptoms beyond 6 months.[11,14]

SCD severity and clinical presentation depend on several genetic and environmental factors. One such factor is the level of HbF, which is said to be protective in infancy as it stops the sickling of erythrocytes under stress, hence a high percentage of HbF is desirable. However, if converted to HbA faster than expected due to possible genetic mutations or other factors, a patient could present with clinical symptoms of SCD earlier than 6 months old. This is especially true for patients with HbSS genotype, which could explain why this patient presented with symptomatic anemia at 10 weeks of age, much earlier than expected.[15–17]

No family history of SCD or recurrent anemia on both the maternal and paternal sides was noted at the time of presentation, similar to findings in a study by Paydas,[18] a case series on SCD and hematological neoplasms. This was, however, only limited to information provided by the mother and grandmother, neither of whom had ever been screened.

The patient presented with severe malaria on his third admission, despite literature suggesting that SCD, to an extent, is protective from severe malaria infection. Arguments are based on the fact that malaria parasites are intra-erythrocytic in nature and so red cell abnormalities would compromise the parasite's persistence.[19] Further, if heterozygous (HbAS) red cells are infected they may easily sickle and thence be targeted for removal by macrophages.[20] This consequently causes lower parasitemia and less severe disease in SCD, while SCA (HbSS) presents as a more fatal disease. Epidemiological studies have supported that SCD is protective (rare or of low parasitemia) from malaria by natural selection or human polymorphism to help preserve the most vulnerable to mortality from the disease.[20–22] In agreement with these studies, Hb electrophoresis results showed that our participant had HbSS, in which severe malaria maybe an occurrence. Clinical presentations of SCD are age-dependent, with more vague features such as dactylitis (swollen hands and feet) and splenic sequestration (abdominal pain and non-specific signs of infection like fever) being dominant in infancy. On the other hand, childhood may be marked by more overt complaints such as pain crisis, priapism, acute chest

syndrome, infections, and neurological manifestations.[23] In contrast with other study findings, our participant did not present with dactylitis at any of the visits, which is said to be the commonest initial SCD presentation.[24,25]

In this report, the child presented with a pneumococcal positive infection at first presentation. Invasive pneumococcal disease (IPD) has largely been reported among children with SCD even among those vaccinated with the pneumococcal conjugate vaccine (PCV).[26] A systematic review of IPD among children with SCD showed a distribution of 61% septicemia, 39% LRTI, and 9% meningitis cases.[27] Similarly, another study by Olufunke et al reported a much higher incidence of the disease among SCD children with a good response to penicillin and from strains not covered by PCV.[6,27] In this case, the child responded well to broad-spectrum antibiotics and was discharged uneventfully.

Staphylococcus haemolyticus showed resistance to multiple antibiotics (Table 1), which was similar to another pediatric study, that also suggested that *S.haemolyticus* was a common nosocomial infection.[28] This may have posed a management challenge as two of the resistant drugs (ciprofloxacin and co-trimoxazole) were among the most readily available and commonly used antibiotics in Zambia.

The widespread introduction of comprehensive care programs providing regular disease monitoring, hematinics, antibiotic prophylaxis, and malaria prevention therapy has led to improved quality-of-life among people living with SCD.[29–32] Additionally, FDA approval of hydroxyurea and more recently crizanlizumab has also helped reduce the frequency of VOCs and improve quality-of-life for sickle patients.[29,33,34] Hydroxyurea is indicated for all patients with HbSS aged ≥ 9 months of age. If scarcely available, it can be given to those with overt stroke, pulmonary hypertension, or renal nephropathy. Regular blood transfusions are recommended for patients with more than three VOC requiring hospitalization per year, recurrent acute chest syndrome, delayed growth, history of stroke, or >2 m/s on transcranial Doppler ultrasound.

In developing countries, access to these interventions and therapeutics remains limited to larger towns and cities. In the case of our patient, the availability of specialized care for children living with SCD may have improved the case outcome and increased access to life-saving treatments such as blood transfusions.

Conclusion

The early presentation of sickle cell disease with severe anemia in this child, although atypical, highlights the importance of newborn screening programs in endemic areas, especially in developing countries. Routinely screening for SCD during the neonatal or infancy period may help improve clinical outcomes through proactive care and disease management. Children presenting with severe anemia as early as 2 months of life should be considered for SCD screening, regardless of family history, by attending clinicians.

Abbreviations

SCD, sickle cell disease; RBC, red blood cell; HbF, fetal haemoglobin; IPD, invasive pneumococcal disease; BCG, Bacille Calmette-Guerin; DPT, diphtheria-pertussis-tetanus vaccine; PCV, pneumococcal conjugate vaccine; OPV, oral polio vaccine; HB, hemoglobin; VOC, vaso-occlusive crisis.

Ethics Statement

Ethical clearance for the parent study was obtained from the University of Zambia Biomedical Research ethics Committee. Written informed consent was obtained from the participant's mother for study participation and publication of case details. The case details cannot be made publicly available because it contains human research participant data; however, de-identified data can be made available to any interested researchers upon request through the Centre for Infectious Disease Research in Zambia (CIDRZ) Ethics and Compliance Committee. To request data access, one must write to the Secretary to the Committee/Head of Research Operations through this email address: info@cidrz.org, mentioning the intended use for the data, contact information, a research project title, and a description of the analysis being proposed as well as the format it is expected. The requested data should only be used for purposes related to the original research or study. The CIDRZ Ethics and Compliance Committee will normally review all data requests within 48–72 hours (Monday–Friday), and provide notification if access has been granted or additional project information is needed.

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Disclosure

All authors report no conflicts of interest in this work.

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