International Medical Case Reports Journal

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CASE REPORT

# Sickle Cell Lung Disease in a 9-year-Old Presenting with Wheezing: Investigating Causal Relationships, Asthma or Acute Chest Syndrome

David Mukunya[1,*], Daniel Mawanda[2,*], Rebecca Nantanda[3], Ruth Namazzi[2], Deogratias Munube[2], Mahad Mohamed Ahmed[2], Faith Oguttu[1], Milton W Musaba[4], Sarah Kiguli[2], Phillip Kasirye[2,5]

[1]Department of Community and Public Health, Busitema University, Mbale, Uganda; [2]Department of Paediatrics and Child Health, College of Health Sciences, Makerere University, Kampala, Uganda; [3]Makerere University Lung Institute, College of Health Sciences, Makerere University, Kampala, Uganda; [4]Department of Obstetrics and Gynecology, Busitema University, Mbale, Uganda; [5]Department of Paediatrics, Mulago National Referral Hospital, Kampala, Uganda

*These authors contributed equally to this work

Correspondence: Faith Oguttu, Department of Community and Public Health, Busitema University, Mbale, Uganda, Email faithfaithoguttu@gmail.com



**Background:** Sickle cell disease (SCD) affects about 7.7 million people worldwide, and this has been increasing annually due to an increasing population in sub-Saharan Africa and the Caribbean. Pulmonary complications contribute significantly to mortality due to sickle cell disease. We have frequently heard wheezing in children with sickle cell disease that has responded to beta agonists such as salbutamol leading us to wonder whether this was asthma or a presentation of acute chest syndrome. We present this case to highlight the co-occurrence of sickle cell disease and asthma, and to re-ignite the debate on the whether this is coincidental or causal.

**Case Presentation:** We present a 9-year-old male from Ugandan, with no known history of any chronic illness who presented with a one-day history of abdominal, limb, and chest pain. He had associated yellowing of eyes, palpitations, and difficulty in breathing. The patient had had a long-standing history of difficulty in breathing, worse during the night and cold seasons, relieved by taking prednisolone tablets that were bought over the counter. On examination, he was sick looking, in mild respiratory distress, with moderate pallor and severe jaundice. Investigation showed a low hemoglobin (6.6g/dl) and immunoglobulin E (IgE) levels were 2300 IU/mL (normal range 0.1 to 200 IU/mL). Hemoglobin electrophoresis showed predominantly sickled hemoglobin (HbSS) (71%), and low fetal hemoglobin (HbF) (8.3%). Spirometry showed an increase of forced expiratory volume after bronchodilator therapy of 22.8%. We made a diagnosis of sickle cell disease and asthma and managed the patient using oxygen, fluid therapy, analgesia, salbutamol by nebulization, hydroxyurea, folate, ceftriaxone and a blood transfusion. For the long-term management, we initiated him on hydroxyurea 20.8mg/kg/day, folate, and fansidar. We also prescribed budesonide and formeterol and are in the process of linking him to a regional referral hospital for chronic care.

**Conclusion:** We present a case of a 9-year-old newly diagnosed with sickle cell disease and asthma highlighting that both conditions can occur in the same individual. We diagnosed both during the same visit and cannot comment on what manifested first. Our findings reinforce the importance of objective pulmonary function testing and allergic evaluation when assessing wheezing in children with SCD.

**Keywords:** sickle cell anemia, sickle cell lung disease, asthma, pulmonology, spirometry

## Background

Sickle cell disease (SCD) affects about 7.7 million people worldwide, and this has been increasing annually due to an increasing population in sub-Saharan Africa and the Caribbean. Most people living with SCD reside in sub-Saharan Africa.[1] About 300,000 children are born with SCD worldwide and 15,000 children are born with SCD in Uganda annually. The prevalence of sickle cell trait in Uganda is 13.3% and the prevalence of SCD is 0.7%.[2] Unpublished medical records show that sickle cell disease contributes to 14% of all paediatric admissions and 10% of mortality in

https://doi.org/10.2147/IMCRJ.S572195
Received: 4 October 2025
Accepted: 5 February 2026
Published: 8 February 2026

Mulago regional referral hospital. Pulmonary complications such as acute chest syndrome, contribute significantly to mortality due to sickle cell disease.[3,4]

Pulmonary disease in SCD has both acute and chronic components.[5] Acute chest syndrome and pneumonic processes characterize acute lung involvement. Chronic lung disease is characterized by both parenchymal and vascular abnormalities, including abnormal lung function, chronic hypoxia, pulmonary hypertension, diffuse interstitial fibrosis, and cor-pulmonale with right ventricular hypertension.[6]

Both obstructive and restrictive lung function abnormalities have been described in SCD. However, restrictive lung disease has been the predominant picture among children with SCD in low-income countries.[3,6] The restrictive pattern is attributed to repeated lung injury over time, following pulmonary microvascular occlusion, acute chest syndrome, and healing by fibrosis. Pulmonary function tests in SCD commonly show reduced FVC and TLC and a preserved or high $FEV_1$/FVC ratio.[7,8]

Obstructive lung disease in SCD has mostly been attributed to chronic hemolysis and nitric oxide depletion, neutrophil-predominant airway inflammation, and ischemia reperfusion injury.[3] Literature has also come up to suggest that a subset of children with SCD have co-existing asthma with less prominent eosinophilia and elevated immunoglobulin E.[9]

Majority of studies done on sickle cell disease lung disease have been done in high income settings.[3,10] A study in Nigeria showed that children had worse respiratory impairment than children in the United Kingdom.[7] There is need to generate more data from sub-Saharan Africa where the burden of SCD is highest. Early detection, diagnosis and appropriate management of respiratory manifestations of SCD, will also ensure better prognosis among these patients in our setting.

In a study that investigated sickle cell disease patients with an obstructive picture, they concluded that despite a reduction of forced expiratory volume, they did not see increased IgE, exhaled nitric oxide, and response to a methacholine challenge, concluding that the obstructive picture seen was not related to childhood eosinophilic asthma.[11]

Despite this evidence, we have frequently heard wheezing in children with sickle cell disease that has responded to beta agonists such as salbutamol, among children presenting with both acute chest syndrome and routine clinic visits. We are convinced that there could be an association between sickle cell disease and asthma like obstructive airway disease and we present this case to re-ignite this debate.

# Case Description

## History

The patient was a 9-year-old Ugandan male from a peripheral health facility in Midwest Uganda.

He presented with a one-day history of wheezing and chest pain, but no preceding flue like illness and cough. He also complained of generalized abdominal and lower limb pains with no preceding history of trauma. He reported to have travelled from Hoima to Kagadi (close to 200km trip), a day prior to the onset of the above symptoms. He reported no history of fever. His caregiver acknowledged that the patient had been sickly since early childhood with episodes of unexplained body pains accompanied by yellow discoloration of the eyes managed at local health facilities. At 6 years of age, he received a blood transfusion for severe anemia accompanying a febrile illness. Over the past one year he had had multiple episodes of chest pain accompanied with wheezing and difficulty in breathing occurring mostly in the night and or during cold weather. These had always resolved after taking over-the-counter medicines which included prednisolone tablets among others.

He had also resorted to wearing heavy jackets and trousers when it was cold, and had stopped taking part in playing football which would also aggravate the respiratory symptoms. There was no history suggestive of atopic disease including dermatitis/eczema, rhinitis, conjunctivitis, or any other allergic manifestations. He had dropped out of school due to poor attendance arising from the frequent morbid events and after spending 4 years in kindergarten. His parents separated for unknown reasons and he currently lives with his grandparents. There is no known family history of sickle cell disease or asthma.

## Clinical Presentation

The patient was agitated and in mild respiratory distress evidenced by nasal flaring and intercostal recessions. He had moderate pallor of both the conjunctiva and oral mucosa that was also dry but with no ulcerations. The dentition was normal with no carries or cavities. He also had moderate scleral jaundice with no other abnormalities.

His weight was 24 kg, height was 126 cm, body mass index z-score was 0 highlighting absence of wasting, his height for age z-score +2, but he had prominent biparietal bossing of the skull. *Vitals*-Saturation of oxygen was 88% at room air, and the pulse rate was 120 beats/minute. Upon ear nose and throat evaluation, significant findings included grade 2 tonsillar enlargement and no other abnormalities.

In the respiratory system he was noted to be tachypneic, with a respiratory rate of 50 breaths per minute and in moderate respiratory distress evidenced by nasal flaring and intercostal recessions. The chest was of normal symmetry non-tender with a normal percussion note, normal air entry and bronchovesicular breath. In addition, he had bilaterally widespread rhonchi. In the abdomen, he had a palpable liver 5 cm below the coastal margin, non-tender but no palpable splenomegaly. The lower limbs were tender but no other abnormalities were detected. All other systems were normal with the exception of a tachycardia of 105 beats per minute in the cardiovascular system.

The working diagnosis was a 9-year-old with *severe pneumonia, acute severe asthmatic attack and probable Sickle cell disease, complicated anemia and acute chest syndrome.*

Malaria and bacterial sepsis were also considered as differential diagnoses.

## Investigations

Investigations done included; a complete blood count which showed leukocytosis, neutrophilia, severe anemia of 6.6g/dl and eosinophilia of 1.1×10 3/ul (nr 0–0.4). Details are shown in Figure 1. Hemoglobin electrophoresis was performed and a diagnosis of Sickle cell disease was confirmed. Details are shown in Figure 2. Additionally, we assessed for underlying risk for atopic disease with Immunoglobulin E (IgE) testing which yielded positive results of 2300 IU/mL (nr 0.1 to 200UI/mL). Lastly spirometry was performed and a notable change in the Forced Expiration Volume in 1 second (FEV1) of 22.8% was realized with inhaled beta-agonists thereby confirming the diagnosis of. Details are shown in Figure 3. The malaria test was negative but were unable to perform the blood culture for logistic reasons.

## Final Diagnosis

A 9-year-old pre-adolescent with:

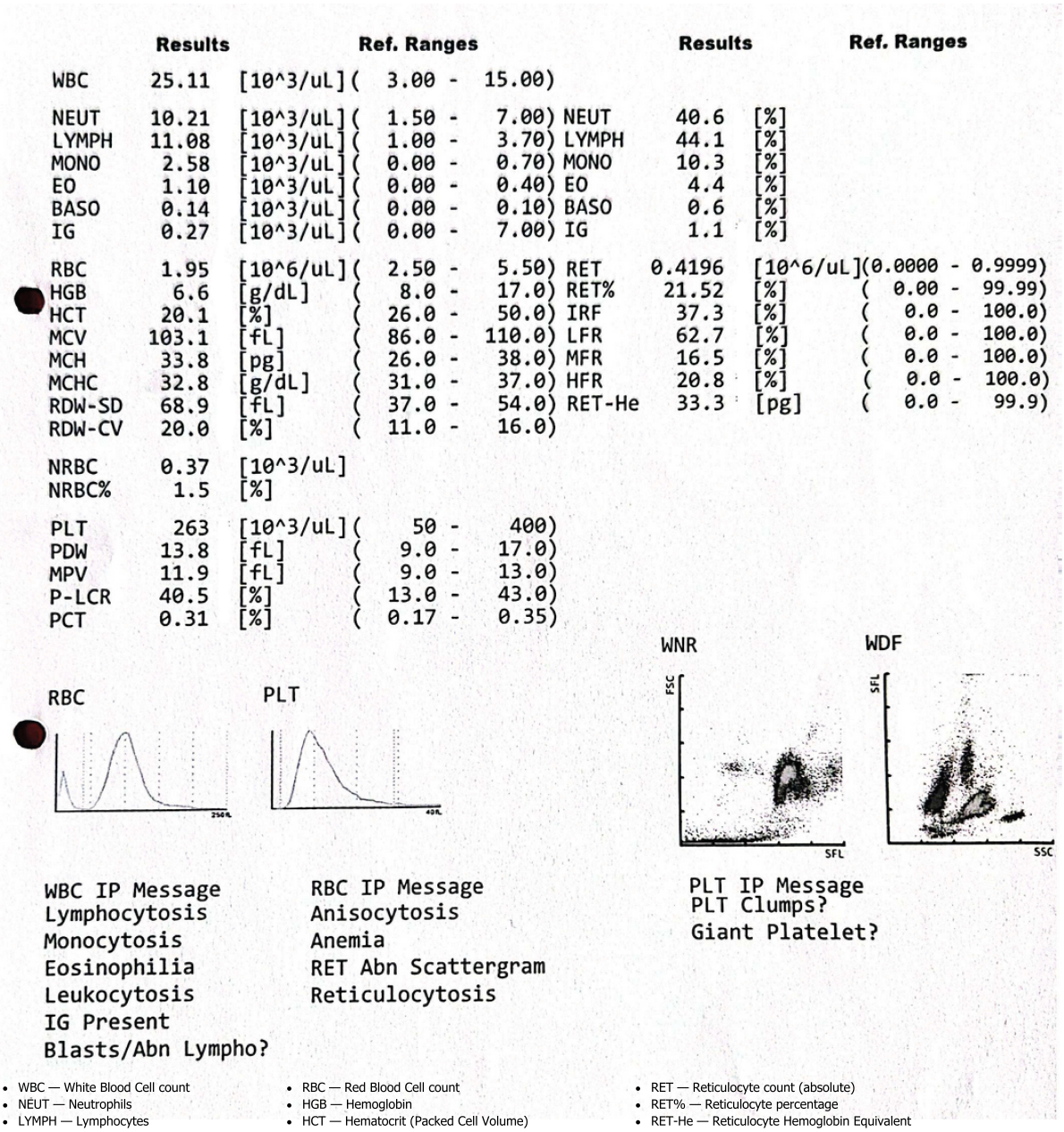
a. Newly diagnosed sickle cell disease (SCD), in vaso-occlusive crisis involving the chest, abdomen and lower limbs.
b. Moderate anemia but was not in congestive cardiac failure.
c. Confirmed clinical features of acute chest syndrome (with hypoxia) and asthma confirmed by spirometry.

## Immediate Management

The vaso-occlusive crisis was treated with paracetamol at 15mg/kg every six hours, combined with ibuprofen 10mg/kg given every eight hours, and oral morphine (1mg/mL) at a dose of 0.4mg/kg every 4 hours. The patient was hydrated using one litre of intravenous normal saline over 24 hours (2/3rds of the total requirement because of the acute chest syndrome).

He was also empirically started on antibiotics- parenteral azithromycin and ceftriaxone for presumed acute chest syndrome, and oxygen given due to the respiratory distress with peripheral tissue hypoxia evidenced by oxygen saturation at 88% on room air.

He also received one unit of blood with packed red blood cells at 10mls/kg given the baseline hemoglobin level of 6.6mg/dl. He was also nebulized with salbutamol at 2.5mg in 3mls of normal saline every 4 hours for one day. Daily folic acid was started at 5mg once a day following the confirmation of sickle cell disease.



| | Results | | Ref. Ranges | | Results | | Ref. Ranges |
|---|---|---|---|---|---|---|---|
| WBC | 25.11 | [10^3/uL] | ( 3.00 - 15.00) | | | | |
| NEUT | 10.21 | [10^3/uL] | ( 1.50 - 7.00) | NEUT | 40.6 | [%] | |
| LYMPH | 11.08 | [10^3/uL] | ( 1.00 - 3.70) | LYMPH | 44.1 | [%] | |
| MONO | 2.58 | [10^3/uL] | ( 0.00 - 0.70) | MONO | 10.3 | [%] | |
| EO | 1.10 | [10^3/uL] | ( 0.00 - 0.40) | EO | 4.4 | [%] | |
| BASO | 0.14 | [10^3/uL] | ( 0.00 - 0.10) | BASO | 0.6 | [%] | |
| IG | 0.27 | [10^3/uL] | ( 0.00 - 7.00) | IG | 1.1 | [%] | |
| RBC | 1.95 | [10^6/uL] | ( 2.50 - 5.50) | RET | 0.4196 | [10^6/uL] | (0.0000 - 0.9999) |
| HGB | 6.6 | [g/dL] | ( 8.0 - 17.0) | RET% | 21.52 | [%] | ( 0.00 - 99.99) |
| HCT | 20.1 | [%] | ( 26.0 - 50.0) | IRF | 37.3 | [%] | ( 0.0 - 100.0) |
| MCV | 103.1 | [fL] | ( 86.0 - 110.0) | LFR | 62.7 | [%] | ( 0.0 - 100.0) |
| MCH | 33.8 | [pg] | ( 26.0 - 38.0) | MFR | 16.5 | [%] | ( 0.0 - 100.0) |
| MCHC | 32.8 | [g/dL] | ( 31.0 - 37.0) | HFR | 20.8 | [%] | ( 0.0 - 100.0) |
| RDW-SD | 68.9 | [fL] | ( 37.0 - 54.0) | RET-He | 33.3 | [pg] | ( 0.0 - 99.9) |
| RDW-CV | 20.0 | [%] | ( 11.0 - 16.0) | | | | |
| NRBC | 0.37 | [10^3/uL] | | | | | |
| NRBC% | 1.5 | [%] | | | | | |
| PLT | 263 | [10^3/uL] | ( 50 - 400) | | | | |
| PDW | 13.8 | [fL] | ( 9.0 - 17.0) | | | | |
| MPV | 11.9 | [fL] | ( 9.0 - 13.0) | | | | |
| P-LCR | 40.5 | [%] | ( 13.0 - 43.0) | | | | |
| PCT | 0.31 | [%] | ( 0.17 - 0.35) | | | | |



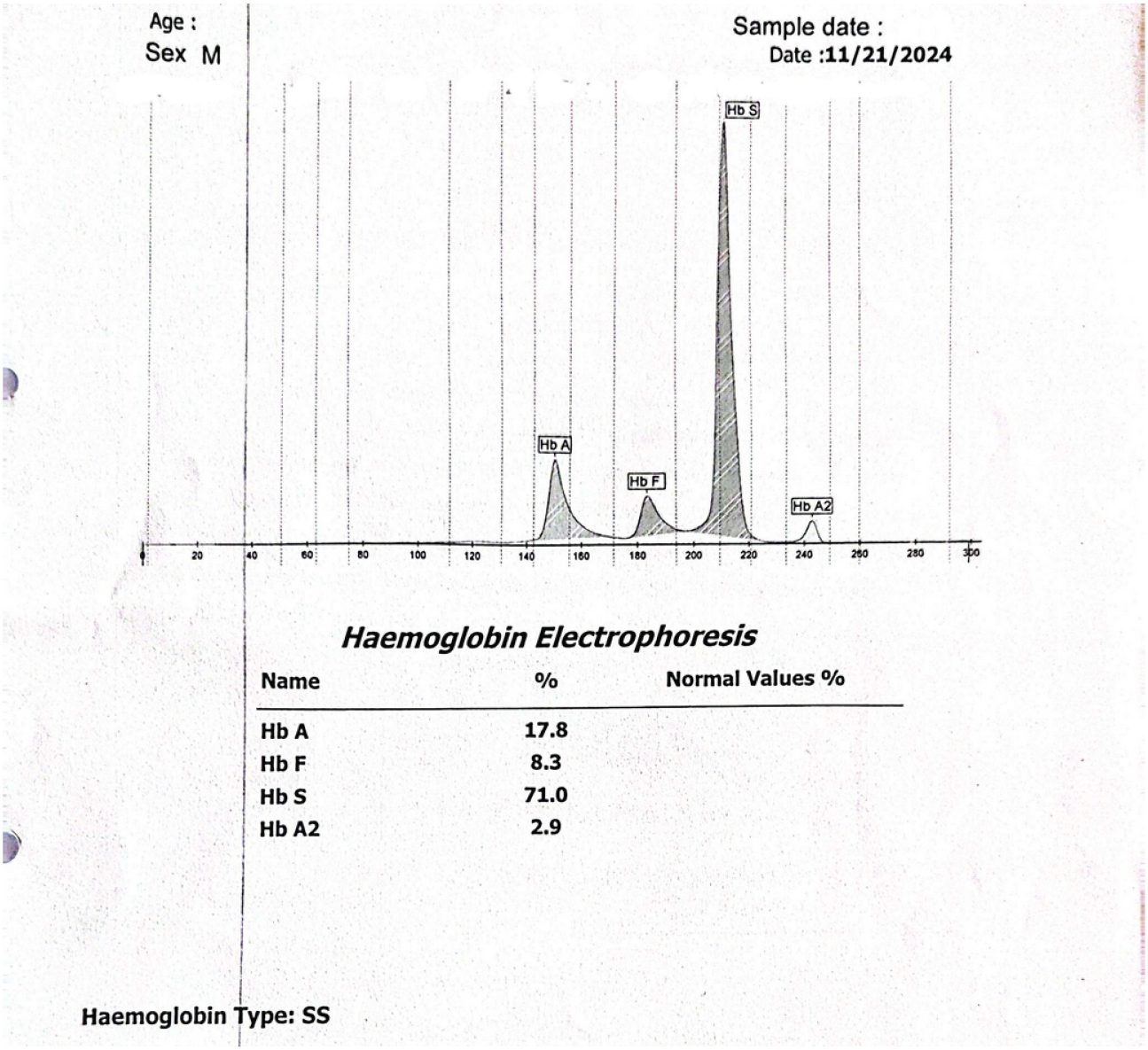
- WBC — White Blood Cell count
- NEUT — Neutrophils
- LYMPH — Lymphocytes
- MONO — Monocytes
- EO — Eosinophils
- BASO — Basophils
- IG — Immature Granulocytes
- PLT — Platelet count
- MPV — Mean Platelet Volume
- PDW — Platelet Distribution Width
- P-LCR — Platelet Large Cell Ratio
- PCT — Plateletcrit

- RBC — Red Blood Cell count
- HGB — Hemoglobin
- HCT — Hematocrit (Packed Cell Volume)
- MCV — Mean Corpuscular Volume
- MCH — Mean Corpuscular Hemoglobin
- MCHC — Mean Corpuscular Hemoglobin Concentration
- RDW-CV — Red Cell Distribution Width
- RDW-SD — Red Cell Distribution Width Standard Deviation)
- NRBC — Nucleated Red Blood Cells (absolute count)
- NRBC% — Percentage of Nucleated Red Blood Cells

- RET — Reticulocyte count (absolute)
- RET% — Reticulocyte percentage
- RET-He — Reticulocyte Hemoglobin Equivalent
- IRF — Immature Reticulocyte Fraction
- LFR — Low Fluorescence Ratio (mature reticulocytes)
- MFR — Medium Fluorescence Ratio
- HFR — High Fluorescence Ratio (immature reticulocytes)

- $\times 10^3/\mu L$ — Thousands per microliter
- $\times 10^6/\mu L$ — Millions per microliter
- g/dL — Grams per deciliter
- fL — Femtoliters
- pg — Picograms
- % — Percentage

**Figure 1** A complete blood count of a 9-year-old boy, with SCD in vaso-occlusive crisis with acute chest syndrome and asthma, showing severe hemolytic anemia (Hb 6.6g/dl) with marked reticulocytosis (RET 21.5%) and reactive leukocytosis (WBC = 25.1 $\times 10^3/\mu L$).




- Hb — Hemoglobin
- HbA — Adult hemoglobin ($\alpha_2\beta_2$)
- $HbA_2$ — Minor adult hemoglobin ($\alpha_2\delta_2$)
- HbF — Fetal hemoglobin ($\alpha_2\gamma_2$)
- HbS — Sickle hemoglobin ($\alpha_2\beta^s{}_2$)

**Figure 2** A hemoglobin electrophoresis report of a 9-year-old boy newly diagnosed with SCD showing, predominant hemoglobin S fraction with residual hemoglobin A and elevated fetal hemoglobin, consistent with sickle cell disease in a transient post-transfusion state.

## Long Term Management

For the long-term management, the patient was initiated on hydroxyurea at 20.8mg/kg/day, daily folic acid at 5mg once a day and monthly malaria chemoprophylaxis of one and half tablets of Sulfadoxine-pyrimethamine. A combined inhaler of budesonide 200 micrograms and formeterol 6 micrograms per puff was prescribed for use once a day.

The patient and care taker were counselled about potential trigger factors which they were advised to avoid. He was discharged after six days following great improvement. The patient was enrolled into a sickle cell clinic for regular review and follow up.

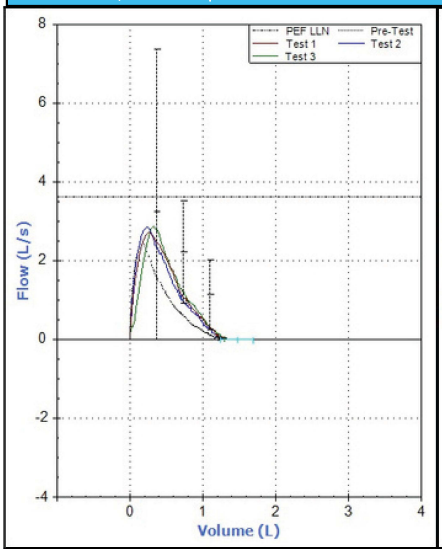

https://doi.org/10.2147/IMCRJ.S572195

Vitalograph®

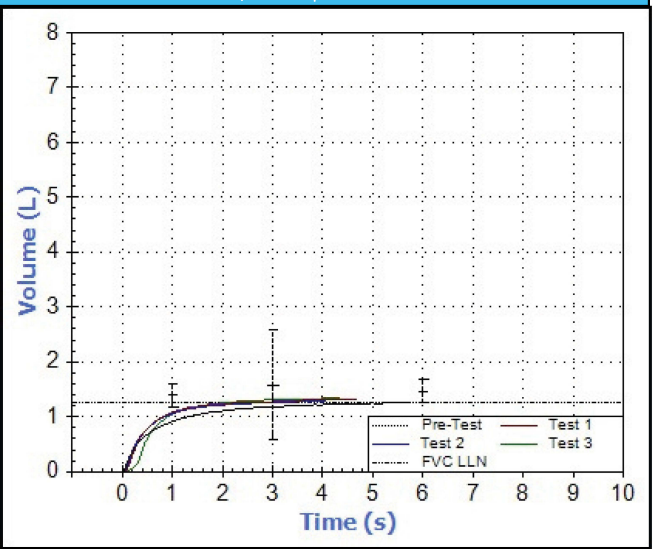
Test Session Information

Pulmonary Function Report - POST Bronchodilator

Flow/Volume Graph




Volume/Time Graph




Results

| Parameter | Pred | Pre Best | % Pre Pred | Post Best | % Post Pred | % Pre Post | Test 1 | Test 2 | Test 3 |
|---|---|---|---|---|---|---|---|---|---|
| FVC (L) | 1.47 | 1.26 | 86 | 1.34 | 91 | 6.3 | 1.33 | 1.28 | 1.34 |
| FEV1 (L) | 1.39 | 0.92* | 66 | 1.13* | 81 | 22.8 | 1.11* | 1.08* | 1.13* |
| FEV1 Ratio | 0.95 | 0.73 | 77 | 0.84 | 88 | 11.0 | 0.83 | 0.84 | 0.84 |
| FEV6 (L) | 1.47 | 1.26 | 86 | 1.34 | 91 | 6.3 | 1.33 | 1.28 | 1.34 |
| PEF (L/min) | 236 | 145* | 62 | 172* | 73 | 18.6 | 164* | 171* | 172* |
| FEF25-75 (L/s) | 2.05 | 0.67* | 33 | 1.22* | 60 | 82.1 | 1.14* | 1.11* | 1.22* |

Values at BTPS ,*Below lower limit of normality (LLN)

Session Quality and Repeatability Information

| Session | FVC Session Grade | FVC Rep: | FEV1 Rep: | Slow Start of test | End of test criteria not achieved | Cough detected in 1st second |
|---|---|---|---|---|---|---|
| Pre | A | 0.02 L (1.5%) | 0.00 L (0.0%) | 1 blow(s) | 2 blow(s) | 0 blow(s) |
| Post | A | 0.01 L (0.7%) | 0.02 L (1.8%) | 0 blow(s) | 0 blow(s) | 0 blow(s) |

Computer Suggested Interpretation

Computer interpretations cannot be relied upon for diagnosis. PRE: Normal ventilatory function. POST: Normal ventilatory function. Slight improvement.

- FVC Forced Vital Capacity
- FEV1 Forced Expiratory Volume in 1 second
- FEV1 Ratio FEV1/FVC Ratio (percentage of FVC exhaled in first second)
- FEV6 Forced Expiratory Volume in 6 seconds
- PEF Peak Expiratory Flow
- FEF25-75 Forced Expiratory Flow between 25% and 75% of FVC (also called mid-expiratory flow or MMEF - Maximal Mid-Expiratory Flow)
- FVC Rep FVC Repeatability
- FEV1 Rep FEV1 Repeatability
- LLN Lower Limit of Normal
- ULN Upper Limit of Normal

**Figure 3** Spirometry results of a 9-year-old boy, with SCD in vaso-occlusive crisis with acute chest syndrome and asthma showing significant bronchodilator responsiveness with $FEV_1$ improvement of 22.8% (1.11L to 1.13L).


https://doi.org/10.2147/IMCRJ.S572195

## Discussion

We present a case of a 9-year-old male with newly diagnosed sickle cell disease and asthma. We are confident that this was asthma primarily because of the positive spirometry finding of an increase in the $FEV_1$ of 23% after bronchodilation administration. This exceeds the ≥12% reversibility threshold recommended by the Global Initiative for Asthma (GINA) guidelines.[12] Further evidence of atopy was evidenced by the elevated IgE levels, making a case for asthma and not a variant of acute chest syndrome.

Our findings are supported by cohort studies, which have reported cases of asthma in more than a quarter of children with sickle cell disease.[3,13] Arigliani et al describes true asthma with demonstrable bronchodilator reversibility among children with SCD. The obstructive defects with significant bronchodilator responsiveness observed reflect co-existing asthma rather than SCD-related airway disease alone.[3]

### Lung Disease Patterns in Sickle Cell Disease

For many years, the traditional teaching has been that SCD is associated with the development of a restrictive lung defect.[6] Where an obstructive picture has been demonstrated, it has been argued that this differs from the typical childhood eosinophilic asthma, suggesting an alternative SCD-related airway pathology.[11] This case challenges the traditional view that obstructive lung disease in SCD is fundamentally distinct from classical asthma.

### Evidence Supporting Asthma in Sickle Cell Disease

Whether wheezing in sickle cell disease is a suggestive of underlying risk for asthma or a manifestation of a variant of acute chest syndrome remains an area of ongoing debate. However, Leong et al demonstrated increased response to bronchodilator therapy among children with sickle cell disease even in the absence of clinical symptoms.[14] He ascribed this to hyper airway reactivity among children with sickle disease and did not commit to the etiology.

Knight-Madden et al moved a step further and assessed for atopic asthma among children with sickle cell disease in Jamaica and compared this to controls,[15] reporting a high incidence of asthma of 48% among children with sickle cell disease compared to 22% among matching controls without sickle cell disease.[15] Moreover, among children with sickle cell disease who had multiple episodes of acute chest syndrome, atopic asthma was far more common (53% versus 12%) as compared to the children who had suffered a single or no episode of acute chest syndrome. Our findings are consistent with the observations reported by Knight-Madden et al in Jamaica.[15]

### Mechanistic Theories Underlying Obstructive Lung Disease in SCD

The etiology of asthma in sickle cell disease remains incompletely understood. One possible hypothesis is that intravascular hemolysis probably triggers a shift in arginine metabolism away from nitric oxide, towards ornithine-dependent pathways, and a proliferative process involving production of proline and polyamines.[16,17] Increased levels of proline contribute to pulmonary fibrosis and airway remodeling because proline is required for collagen synthesis.[17] Similar mechanisms are partly responsible for the structural remodeling of lungs seen in asthma patients.[18–21]

### Strengths and Limitations

A key strength of our case is that we conducted both spirometry and measured IgE levels, having stronger evidence for asthma. However, we did not assess for atopy using skin prick tests, and this could have added to the confidence in an asthma diagnosis.

However, since we only report a single case, our findings have limited generalizability to other patients. In addition, spirometry and clinical features in children with sickle cell disease may be influenced by concurrent or recent acute chest syndrome, which can transiently affect lung function and mimic or exacerbate obstructive findings. Although there was no clear clinical evidence of acute chest syndrome at the time of assessment, its potential impact cannot be entirely excluded.

Other potential confounders, including intercurrent respiratory infection and exposure to environmental allergens, concomitant medications, may also influence airway inflammation, but were not fully controlled for in this case.

We advocate for quantitative studies assessing for the prevalence of asthma among children with sickle cell disease, particularly those of the sub-Saharan haplotypes, to better define the overlap between asthma, airway hyperreactivity, and acute chest syndrome, and to test this hypothesis.

## Conclusion

We present a case of a 9-year-old newly diagnosed with sickle cell disease and asthma highlighting that both conditions can occur in the same individual. We diagnosed both during the same visit and cannot comment on what manifested prior. Our findings reinforce the importance of objective pulmonary function testing and allergic evaluation when assessing wheezing in children with SCD. We recommend further studies to assess asthma prevalence and pathophysiologic mechanisms among children with SCD in our setting.

## Abbreviations

FEVI, Forced Expiration Volume in 1 second; GINA, Global Initiative for Asthma; IgE, Immuniglobulin E; SCD, Sickle cell disease.

## Ethics Approval and Consent to Participate

The article describes a case report. Therefore, no additional permission from our Ethics Committee was required.

## Consent for Publication

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images.

## Acknowledgments

We would like to acknowledge the participant and his caretaker for consenting to have their unique case documented and published.

## Funding

This research study was funded by "National Institutes of Health's, FOGARTY INTERNATIONAL CENTER" to Enhancing Research Capacity for Sickle Cell Disease and related NCDs across the Lifespan in Uganda, Enrich Project under award number D43TW012466. The funders had no role in study design, implementation and data analysis.

## Disclosure

The authors have no competing interests to declare for this work.

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