

## Case report

### Socioeconomic Status as a Determinant of Delayed Diagnosis of SCD - A Case Report of Newly Diagnosed SCD in a 52-Year-Old Woman

**Comment [U1]:** Check for author instructions and modify accordingly i.e. Papers should not exceed 2000 words

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#### Abstract

A look into the associations of socioeconomic status (SES) with the prevalence of various complications in sickle cell disease (SCD) is necessary to improve societal norms, governmental health policies, and strategies. A person's social standing in a society is generally governed by the combination of his education, profession, and income, which is regarded as his SES. Considerable evidence establishes the likelihood of individuals from low SES suffering from the disease, cognitive problems, and increased mortality (Lubeck et al., 2019, National Research, 2004). Sickle cell disease (SCD) is one of the most common severe genetic hemoglobinopathies that the World Health Organization has recognized as a global public health problem. Socioeconomic status (SES) is defined as an individual's social or economic standing and is a measure of an individual's or family's financial position or rank in a social group. Current guidelines and management algorithms of SCD do not factor in the effect of SES on patients with SCD. There is a lack of literature regarding the role of SES and its impact on clinical outcomes and characteristics of SCD. Studies have shown that lower SES is linked to disproportionate access to health care in many diseases, and of all the factors that measure SES, income was the most indicative.

**Comment [U4]:** Provide brief abstract of case in the abstract and minimize the given general description

**Keywords:** Sickle cell disease; health disparity, complications; socio economic status; sickle cell anemia.

#### Introduction

Sickle Cell Disease is an inherited disorder of hemoglobin caused by an abnormal hemoglobin molecule, hemoglobin S (HbS), which results in the sickling of red blood cells. HbSS is the most common and severe type of SCD found in Nigeria, including SS, SC, and HbS $\beta$ thalassemia [1][2]. Its spectrum of clinical symptoms is classified into vaso-occlusive, hemolytic, acute chest syndrome, and aplastic crises. SCD is often diagnosed in infancy, usually, after six months of life, when fetal hemoglobin F (HbF), which conferred protection from sickling during the intrauterine period, would have cleared off. This is also why genotype testing is unreliable until after this period [3]. It is a hemoglobinopathy of public health importance, with Nigeria holding a strategic position having the largest population of people with sickle cell disorder, with about 150,000 of 300,000 annual global births [1]. Despite the humongous burden of SCD, many cases in Nigeria are not diagnosed early, and some people eventually go undetected into adulthood. In a retrospective study of children with sickle cell disease who attended the children's outpatient department of the University College Hospital, Ibadan, Nigeria, between June 2000 and June 2009, case notes of 457 children with SS and SC phenotypes of HbS were reviewed in 2009, it was discovered that the median age at diagnosis of the disease was 2.0 years (2.5months -14.0 years) [4]. It will be essential to note that the researchers considered a maximum period at diagnosis of 14 years as found in their study a late presentation and this goes to highlight our interest in the case under review. In this report, we present a case of a Nigerian woman of the Ijaw tribe whose condition was not

diagnosed until after 52 years, a husband heterozygous for the sickle cell trait, 11 uncomplicated parous experiences despite well-documented literature on obstetric complications and maternal mortality in SCD patients [5]. In addition, five child deaths (mainly under the age of 5), several episodes of bone pains for which she regularly visited local drug stores for over-the-counter pain relief, one defining clinic visit, and subsequent genotype testing, which eventually led to the diagnosis of her condition. We will also highlight the pathophysiology and management of the condition and the biological and socio-economic factors that may have led to her late diagnosis.

### Learning Objectives

Upon completion of the chapter, the reader will be able to:

Explain the underlying causes of sickle cell disease (SCD) and their relationship to patient signs and symptoms.

Identify the typical characteristics of SCD as well as symptoms that indicate complicated disease.

Identify the desired therapeutic outcomes for patients with SCD.

Recommend appropriate pharmacotherapy and nonpharmacotherapy interventions for patients with SCD.

Recognize when chronic maintenance therapy is indicated for a patient with SCD.

Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for SCD.

Educate patients about the disease state, appropriate therapy, and drug therapy required for effective treatment and prevention of complications. However, the mission is to improve the quality of life of those suffering with sickle cell disorders and to inform and educate the general population about the disease.

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### Case Report

We present the case of a 52-year-old woman who came to the outpatient clinic complaining of a 4-day history of leg pains and weakness. Leg pains were so severe, rendering her unable to walk unaided (with a score of 8/10 on the pain scale). There was no prior history of trauma; however, there was a history of recurrent painful episodes involving different parts of her body since childhood. Symptoms were usually managed with over-the-counter pain medications (including NSAIDs) and herbal medications and resolved after about a week of self-treatment. She never sought care at a medical facility but often resorted to herbal treatments, sometimes involving scarifications on the pain sites. There was no past or recent history of yellowing of the eyes or cola-colored urine, and she had never been haemo-transfused before this visit. She has a history of recurrent heartburn and epigastric pain but no history of melena stools, hematochezia, or weight loss. She still had regular menstrual periods, with a history of menorrhagia two months before the presentation. She has had 11 full-term pregnancies, none of which were monitored at an antenatal clinic. Five of her children died within the first five years of life due to

'unexplained illnesses,' and one died in the early neonatal period due to complications of neonatal jaundice. She had never received formal education and worked as a petty trader (sold smoked fish). Her husband was also an unskilled worker with no formal education. They both lived in a village in south-south Nigeria without close access to secondary or tertiary medical facilities.

She came along with her husband, who stated that a day before the presentation, she had undergone some blood tests, including a complete blood count, at a stand-alone laboratory which revealed a PCV of 21% and was advised to visit the hospital immediately. At the presentation, she looked acutely unwell, was in apparent painful distress, and was pale. However, she was not jaundiced, afebrile, or in respiratory distress. Her vital signs were all within normal range. Examination of the chest was unremarkable, while that of the abdomen revealed scarification marks but no hepatomegaly or splenomegaly. There was no swelling or differential warmth on the legs; however, there was some tenderness and impaired mobility because of the pain. A repeat complete blood count confirmed severe anemia (PCV 20%) and neutrophilia. Other findings of the total blood count were as follows – White Cell Count:  $6.7 \times 10^3$  cells/uL (standard), Neutrophils: 67.4% (elevated), RBC: 3.20 (low), MCV: 63.2 (below average), MCH: 20.8 (below average), Platelet Count:  $145 \times 10^3$  cells/mm<sup>3</sup> and the calculated Mentzer index: 19.8. A urine dipstick was done with the following results – Appearance: Cloudy yellow, protein (+), Specific Gravity (1.030), Leucocytes (++) , Urobilinogen (Normal), Nitrite (Nil), Blood (+++), Bilirubin (Nil), Ascorbic Acid (Nil). HIV antibody test was negative, malaria parasites were seen on a blood film (+), and Random Blood Glucose was 113mg/dl. A hemoglobin genotype test revealed HbSS. Her husband was also counseled to undergo the genotype test, to which he consented, and it showed a sickling trait (HbAS). Before this, neither had been tested for their hemoglobin genotypes. Note that the range of lab tests was limited due to financial constraints.

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A diagnosis of vaso-occlusive crisis in a newly diagnosed case of the sickle-cell disease was made. She was also treated for malaria, uninvestigated dyspepsia, iron-deficiency anemia (secondary to possible menorrhagia and NSAID-induced chronic gastritis), and urinary tract infection. She was haemotransfused with three units of packed red blood cells. She was placed on IV fluids (and encouraged to hydrate orally), analgesics (IV Tramadol infusion, IV Paracetamol), antibiotics (IV Ceftriaxone), antimalarial (IM Arteether), Folic acid 5mg, a proton-pump inhibitor (IV Omeprazole) and a suspension antacid. Symptoms decreased within the first 36 hours, and a post-transfusion PCV was 35%. After being thoroughly counseled on the condition, she was fit for discharge on day 3 of admission. She was discharged on malaria prophylaxis (Proguanil), antacids, analgesics, folic acid, and oral antibiotics and scheduled for a follow-up visit in a week.

## Discussion

Sickle cell disease (SCD) is a hemoglobinopathy underpinned by the inheritance of two abnormal hemoglobin genes, with at least one being Hemoglobin S (HbS). It is one of the most common severe monogenic disorders known to man [1,2]. SCD is characterized by chronic hemolytic anemia and vaso-occlusive phenomena [3,4]. Diagnostic methods for sickle cell disease are age-specific. Methods useful for early diagnosis tend to be more costly and so not readily available in Africa, which has the highest burden of sickle cell disease but is present universally in England and the USA. [5] Hemoglobin analysis forms the bedrock of the diagnosis of sickle cell disease [6].

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Overall, DNA-based testing is used for prenatal diagnosis. After birth, protein-based methods like Hb electrophoresis, which is widely available, become the test of choice [7,8,9]. Hb separation techniques like high-performance liquid chromatography, where available, are preferred to Hb electrophoresis as they are precise in identifying and quantifying various hemoglobin types. They are confirmatory as well [10]. In areas with high disease burden, diagnosis is often suspected at six months of age when many affected children present with classical symptoms of sickle cell disease: dactylitis, severe anemia, recurrent infections, abdominal swelling from enlargement of hematopoietic organs: liver and spleen. A full blood count, a common initial test, usually reveals anemia with leukocytosis. Microcytosis may either reveal concomitant thalassemia or iron deficiency anemia [11,12]. Citrate acetate electrophoresis is the most common test for sickle cell disease. This is what was used in the index case.

Isoelectric focusing is a more sensitive variant of standard electrophoresis. This has been employed in many newborn screening programs. Currently, point-of-care testing kits have shown great promise in early diagnosis. The Hemotype SC kit, which uses monoclonal antibodies to differentiate normal adult Hb (HbA), Hb S, and Hb C, has shown more reliability. It is relatively affordable and promises to transform the early diagnosis of sickle cell disease, especially in Nigeria, which has the highest burden of SCD worldwide [13]. Where thalassemias are suspected, quantification of hemoglobin A2 makes the diagnosis clearer. Despite all the advances made in diagnosing sickle cell disease, there is more to be done to explain the varying phenotypic expressions in people with sickle cell disease. For example, the protective factors that made our patient arrive unusually late [14].

### **Treatment**

For individuals with SCD, VOCs are the most frequent cause of ED visits and hospitalizations. One of the most crucial aspects of offering high-quality treatment to patients with SCD in the ED is ensuring that patients receive prompt, efficient pain relief. The patient's journey starts when they present to the ED, with some patients continuing to hospital admission. It is successful when they are discharged home and includes an additional 30 days after leaving the hospital (ED or inpatient unit). Care that adheres to best practices has been provided outside of an ED setting in other jurisdictions (Florida, Georgia) and in one Ontario pilot study. However, most initial care in Ontario is provided in an ED setting. The ED is referred to frequently throughout the best practice recommendation, as that is the current situation in Ontario. It must be emphasized, though, that these suggestions apply to any setting that can offer the evaluation, care, and oversight needed to treat patients with VOC. Optimal VOC management influences future management decisions and provides the chance to establish confidence. Upon presentation at the Emergency Department, an initial assessment was made, necessitating admission. Intravenous access was secured, and blood samples for laboratory investigations were taken. The patient was immediately commenced on opioid analgesic (tramal infusion) and intravenous fluids for rehydration. Upon review of her investigation results, antibiotics and antimalaria were added to her medications. She was transfused with three units of whole blood on account of a Packed Cell Volume (PCV) of 20%. The patient was on admission for three days. The result of the hemoglobin genotype was released on the 2nd day of admission, and the patient was informed about the outcome of the test and counseled on the diagnosis. Her clinical condition improved remarkably on the 3rd day of admission, post-transfusion pcv was 36%. She was discharged on analgesics, hematinic, and malaria chemoprophylaxis and scheduled for a follow-up visit in 1 week.

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### *Analgesic history:*

The patient should be well-prepared with self-management training and a care strategy for early-stage VOC. The patient should bring their medicine and a record of their self-administration to the emergency department. 3 Ps of Pain Management:

*Physical pain techniques* (e.g., massage, warm blankets/heat packs to the affected area, stretcher adjusted to the position of comfort, quiet surroundings, etc.).

*Psychological techniques* (e.g., emotional support, behavior management, distraction with music, video games, TV, etc.); minimization of psychological stress related to provider interactions/environment (e.g., behaviors that are not empathetic add to psychological stress, which makes it more challenging to manage pain). Pharmacological treatment and hydration are the cornerstones of the management of VOC.

### **Principles of Acute Pain Management**

*Rapid assessment to establish that the patient has a VOC.*

Aggressive pain management using the appropriate dosage of opioids, which will be decided by (a) whether the patient has taken opioids at home to treat this episode, (b) whether the patient has chronic pain that is treated with opioids, and (c) the dosages that the patient has previously received in the ED to treat their pain. Opioids should be gradually increased until they provide effective pain relief, as determined by a reliable pain assessment instrument. It is best to start therapy with an intravenous bolus and administer repeat doses every 15-20 minutes to relieve pain (while assessing for pain relief and sedation). If rapid IV access is not possible, the patient may begin opioid therapy using any other method (e.g., oral, SC, intranasal).

*Rapid and aggressive use of the patient's "opioid of choice"* indicates patient-centered pain control. Analgesia should be chosen based on a pain assessment, accompanying symptoms, outpatient analgesic use, patient awareness of efficient agents and dosages, and prior side effect experience. There is no universally relevant or successful medication, dose, administration route, or frequency for all patients.

*Multimodal pain management:* "This approach simultaneously administers two or more analgesic agents with different mechanisms of action. Combination therapy using drugs with distinct mechanisms of action may add analgesia or have a synergistic effect and allow for better analgesia with the use of lower doses of a given medication than if the drug were used alone [15].

### *Analgesics and adjuvants*

The effectiveness of analgesics varies from person to person. Treatment should include a standard opioid approach with options available for patients who have had reactions to one opioid or have had better results from one opioid over another. Non-steroidal anti-inflammatory medications (NSAIDs) such as ibuprofen at home and ketorolac (parenterally) in the hospital are recommended as adjuvant medications without contraindications. Acetaminophen can be added as well if there are no contraindications [15]. Over time people with SCD develop chronic diseases related to tissue and organ damage; some medications will not be recommended when specific organ damage is present. Manage

side effects, most commonly nausea, pruritus, and sedation. Be aware of other sedative effects from medication used to manage side effects, e.g., dimenhydrinate and diphenhydramine.

#### *Dose*

Titrated intravenous bolusing of opioids to effect is recommended. Delivering frequent (every 15- 20 minutes) boluses in the initial phases of treatment in acute care (usually the ED) provides a rapid systemic effect. The patient should be monitored as per organization policy following the administration of opioids. The goal for patient care is that they receive prompt attention and safe and effective pain management. Once pain control has been achieved, opioids can be given regularly to provide longer-term analgesia (e.g., oral long-acting formulations, transdermal patches, or continuous IV infusions) with appropriate orders for breakthrough dosing. The evidence supports this aggressive management of acute pain [16]. Attention must be given to equivalence when converting a route or drug. Emergency department length of stay among those with SCD VOC is reduced with rapid, aggressive pain management with opioids. Dose ranges should be standardized for the opiate naïve. People with SCD can develop chronic pain, and their requirements might be much higher than with opioid naïve patients.

#### *Route*

Options for the route of administration should be identified for analgesics. Intravenous delivery of opioids is optimal for the initial management of acute pain in the ED; however, difficulties starting an intravenous can sometimes occur. This should not delay opioid administration. Alternate delivery can provide bridge dosing while a clinician with the expertise to place the intravenous catheter is located and arrives at the bedside. Intranasal, subcutaneous, and oral, including sublingual routes, should all be considered [16].

"I have a routine- hot shower, fluids, rest, my family will massage me, but after 24 hours, if the pain moves to another place, I know I have to get to the hospital. I've had this all my life, I have no veins left, and I tell them that, and they say, oh, we have someone good (at starting IVs),' and an hour later, i have had 12 pokes and no pain medication, not even anything orally." Patients may present with central venous access catheters in place; ED clinicians must have access to clinicians with expertise in working with these lines. While waiting for support, alternate routes of opioid administration should be used to provide bridge dosing. Patient-controlled analgesia (PCA) is recommended for patients who are competent to manage PCA and are in environments where clinicians can initiate PCA. Oral PCA has been used in the appropriate settings with patients carefully selected for their ability to take their analgesic as required [17] and record their utilization. Both patient-controlled options require careful patient selection, clinician education, resources, and processes to ensure safety. Organizations with long waits from discharge disposition to transfer to an inpatient bed should ensure the transfer of care to an inpatient physician/service as quickly as possible. In the interim, the emergency physician should write standing orders for analgesia during the waiting time of transfer of care to an inpatient consultant to avoid lengthy times of no analgesia [18]. A process should be developed to support patients with the delivery of pain medication and monitoring in the least noisy and stressful environment possible, reducing the negative environmental impact on the patient's ability to rest and sleep while awaiting consultation and transfer to an inpatient bed.

#### *Patient Self-Management:*

People with SCD and their families need education on recognizing the onset of a VOC and the physical, psychological, and pharmacological self-management measures to take. Understanding one's patterns and experiences to manage them is critical to living with SCD. Patients are encouraged to keep a pain diary and have an action plan should the pain become unmanageable at home. Patients should be educated about common triggers for VOC and work with healthcare team members to develop prevention strategies [19]. All patients with SCD should have a home care/action plan developed with their SCD provider. The plan should include the following: (i) A reminder of warning symptoms that should prompt urgent ED/SCD team care (fever, chest pain, shortness of breath, signs of stroke, splenic enlargement, etc). (ii) Steps to manage pain, analgesia type, dose and frequency, hydration, warm blankets or warming pads, quiet and a stress-free environment. (iii) Support of family member or advocate. (iv) Contact information for an SCD provider for advice and consultation. (v) Plan on how to travel to their regular hospital. (vi) Details of the VOC, including what treatments have been implemented (i.e., the name, dose, and timing of oral pain medications at home), should be documented and brought to the hospital if necessary. Providers should understand that VOC can and will occur despite informed and conscientious self-management [20-23].

## Conclusion

Sickle cell disease (SCD) is an inherited disorder of hemoglobin structure that has no established cure in adult patients. Cure has been achieved in selected children with sickle cell anemia (SCA) using allogeneic bone marrow transplantation or cord blood transplantation. SCD is essentially a triumvirate of (1) pain syndromes, (2) anemia and its sequelae and (3) organ failure, including infection. Pain, however, is the hallmark of SCD and dominates its clinical picture throughout the life of the patients. The prevalence of these complications varies with age from infancy through adult life. However, pain, infections and anemia requiring blood transfusion occur throughout the life span of affected patients. The overall medical care of patients with SCD in developed countries has improved such that their life expectancy has almost doubled since 1951. Currently, there are at least five major approaches for the general management of SCD and its complications. These include (i) symptomatic management, (ii) supportive management, (iii) preventive management, (iv) abortive management, and (v) curative therapy.

Comment [U9]: Concise the conclusion part

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