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Socioeconomic Status as a Determinant of Delayed Diagnosis of Sickle Cell Disease - A Case Report of Newly Diagnosed Sickle Cell Disease in a 52-Year-Old Woman

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

A look into socioeconomic status (SES) associations with delayed diagnosis of 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 recognized by the World Health Organization as a global public health problem. Socioeconomic status (SES) is an individual's social or economic standing and measures 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 needs to be more 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.

Keywords: Sickle cell disease; health disparity, complications; socioeconomic status; sickle cell anemia.

1. 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 HbSβthalassemia [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 enormous 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. This highlights 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, six 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 disease and the biological and socioeconomic factors that may have led to her late diagnosis.

2. 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 x 103 cells/uL (standard), Neutrophils: 67.4% (elevated), RBC: 3.20 (low), MCV: 63.2 (below average), MCH: 20.8 (below average), Platelet Count: 145 x103 cells/mm3 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.

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 haemo-transfused 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.

3. DISCUSSION

The patient presented in this case report was born and raised in a rural village in the riverine area of Warri – a city in the South-South of Nigeria. Nigeria accounts for about a third of the global burden of sickle cell disease [6]. With sickle-cell disease being among the most common inherited disorders globally, routine newborn screening has been implemented in the U.S. and most European countries [7]. This has helped to reduce the occurrence of delayed diagnosis of the disease. However, numerous factors have contributed to the difficulty in implementing such a policy in Nigeria, including the absence of budgetary allocation, erratic power supply, and limited qualified personnel and screening facilities [8]. According to Claeys et al. (2021), factors influencing the age of presentation of SCD include the following: Doctor's delay, patient's delay (including education, the financial position of the parents, and cultural beliefs about the illness), Fetal hemoglobin, Reticulocyte count, and Genetic modulators such as SCD genotype, Alpha-thalassemia, and Fetal hemoglobin concentration [9]. For this paper, we would like to group these factors into modifiable and non-modifiable risk factors for delayed diagnosis of sickle cell disease. The modifiable risk factors are directly linked to the patient's socioeconomic status.

In this case, the socioeconomic determinants that may have contributed to her late presentation are highlighted below: (i) Poor educational background: In addition to the fact that she has had little to no formal education, most people in her community are not only poorly educated but are also underserved – with regards to health advocacy and promotion. Hence, limited access to health-related information could have led to her understanding of her recurrent symptoms and timely seeking medical care. (ii) Financial status: The patient came from a humble background. As a fish seller with minimal income, she could not afford primary medical care and instead sought treatment from the more readily available and cheaper herbal practitioners. (iii) Cultural perspective about the disease: Like in many rural communities in Nigeria and other parts of sub-Saharan Africa, there is a strong belief in the use of herbs and spiritual rites to cure illnesses – especially recurrent ones which are seen as 'spiritual attacks,' as in the case of SCD. This has further removed the need for them to seek orthodox treatment, which the majority sees as a waste of time. (iv) Poor health-seeking behavior: Even though newborn screening programs for SCD are not fully operational in most African countries, there are other avenues by which the disease is picked up. Apart from the typical case of a patient presenting with suggestive clinical features, several people with the trait and disease are diagnosed during pre-marital screening (which, in recent times, many religious bodies have started instituting as a requirement before carrying out the marriage ceremony) and antenatal screening. Unfortunately, neither she nor her husband got screened before they married or had children, missing the opportunity to identify their genotypes. Although maternal health advocacy has gradually taken the forefront in the public health sphere in Nigeria and most African countries, many rural communities are yet to be captured by these programs. For example, in our index case, none of her 11 pregnancies were registered or monitored at the antenatal clinic, thereby missing multiple opportunities for her hemoglobin genotype to be identified. Her poor health-seeking behavior also might have led to the possible loss of 5 of her children to complications of the disease. (iv) Geographical location: Because of the poor transport routes and limited health funding allocated to the riverine communities in the Niger Delta region of Nigeria, there is relatively poor access to standard healthcare, screening programs, and health promotion in such areas. This patient living in one such community might also have contributed to her delayed diagnosis.

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].

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]. Where available, Hb separation techniques like high-performance liquid chromatography 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 complete blood count, a standard 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]. For individuals with SCD, vaso-occlusive crisis are the most frequent cause of emergency department (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 emergency department, 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 emergency department 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 a vaso-occlusive crisis. Optimal vaso-occlusive crisis management influences future management decisions and provides the chance to establish confidence.

Analgesic history: the patient should be well-prepared with self-management training and a care strategy for an early-stage vaso-occlusive crisis. 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 managing the vaso-occlusive crisis. 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 emergency department to treat their pain. Opioids should be gradually increased until they provide adequate 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). Prompt 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 using lower doses of a given medication than if the drug were used alone [15]. 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 also be added 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. A titrated intravenous bolus 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 vaso-occlusive crisis 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. Options for the route of administration should be identified for analgesics. Intravenous delivery of opioids is optimal for initial acute pain management in the emergency department; 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].

4. CONCLUSION

Sickle cell disease is a subject of extensive study requiring more research; it can manifest in children in various ways and at different stages of life if there has not been any neonatal screening and it is due to various circumstances. A proper understanding of the factors that leads to late presentation and diagnosis needs to be well understood to achieve early diagnosis, prompt treatment and improved quality of life.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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