The Bias of Medicine in Sickle Cell Disease

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ABSTRACT

Sickle cell disease (SCD) is the most common monogenetic condition in the United States (US) and one that has been subjected to a history of negative bias. Since SCD was first described approximately 120 years ago, the medical establishment has, directly and indirectly, harmed patients by reinforcing biases and assumptions about the disease. Furthermore, negative biases and stigmas have been levied upon patients with SCD by healthcare providers and society, researchers, and legislators. This article will explore the historical context of SCD in the US; discuss specific issues in care that lead to biases, social and self-stigma, inequities in access to care, and research funding; and highlight interventions over recent years that address racial biases and stigma.

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HISTORY OF SICKLE CELL DISEASE IDENTIFICATION AND TREATMENT

Sickle cell disease (SCD) is one of the world's most common monogenetic disorders.[1, 2] It affects approximately 100,000 individuals within the United States (US).[3] The prevalence of SCD is unequally distributed across race, a social construct without clear biologic underpinning but with social implications.[4, 5] Though SCD is not specific to one race, people who identify as Black Americans are disproportionately affected in the US. Based on newborn screening results, approximately 1 out of every 365 Black American newborns are affected by SCD.[3]

This disparity is reflective of SCD's history within the US, which is marked by medical racism and racialized science. In 1904, Ernest Irons and James Herrick noted "sickle-shaped" erythrocytes in a Grenadian dental student named Walter Clement Noel.[6, 7] Inspired by Herrick's original 1910 article, Victor Emmel developed a diagnostic test for detecting "sickled" erythrocytes.[8] He interpreted these results as evidence that SCD was a genetic disorder. The medical community extrapolated the findings to argue that SCD was a condition intrinsic to "Negro blood."[9] This was the origin of the myth that SCD is specific to Black American individuals. Though SCD was being reported in White patients, the presence of sickled cells was seen as evidence of "racial admixture" or "miscegenation."[10–13] The belief that SCD was specific to Black Americans was used by physicians as evidence for the "biological superiority" of Whites. This was later used as a justification for segregation, and likely fueled discriminatory practices in blood banking.[9, 14]

As time passed, SCD continued to receive little attention.[15] The medical establishment made little effort to provide Black Americans education on SCD, access to genetic counseling, and medical care in general.[16] In 1969, only 30% of Black Americans surveyed had heard about SCD, and only 20% knew that it was a blood disorder.[17] This lack of awareness left Black Americans affected by SCD disempowered and unable to understand aspects of their health and family planning. In 1972, due to efforts by advocates, the Nixon Administration passed the Sickle Cell Anemia Control Act, which created centers based in medical schools to educate the public on SCD, fuel research endeavors, and address these health disparities.[18, 19] Although the bill's advocacy, education, and research initiatives were widely regarded as successful efforts, since testing results for SCD and sickle cell trait (SCT) were publicly available, subsequent pieces of legislation led to further discrimination. Some states forced Black Americans to undergo mandatory premarital and preschool testing for the SCT without receiving any follow-up counseling, a distortion of the 1972 bill that was meant to empower, not subjugate, patients.[18] Additionally, on a federal level, Black Americans with either SCD or SCT were banned from becoming pilots or co-pilots by the US Air Force.[13, 20]

SICKLE CELL DISEASE SYMPTOMS AND MEDICAL BIAS

SCD manifests with complications such as vaso-occlusive events (VOE), which are intense pain episodes caused by ischemia and inflammation that often require the use of opioid and non-opioid analgesics.[21] VOEs can last from hours to days, and 20% of patients experience a severe pain episode once a month.[22] Approximately 10–20% of patients who are admitted for a VOE will develop acute chest syndrome (ACS), a leading cause of death, within 3 days of hospitalization.[23] Considering these severe complications, 20% of

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patients with SCD require three or more acute care encounters per year, and 30% have a 30-day rehospitalization rate.[24] During hospitalizations, patients may receive multimodal analgesia, antiemetics, oxygen, fluids, blood, and antibiotics for infections, among other treatments.[25]

Due to a lack of standardization, care varies and can be misguided based on distrust of reported pain levels. Patients with chronic pain, as opposed to those without, may not display the same reactions while experiencing acute pain (facial expressions, elevated blood pressure, psychological distress).[26, 27] Frequent hospital visits also lead to inappropriate response times for patients presenting with VOEs. The American Pain Society (APS) states that patients with SCD who seek medication for acute pain should receive treatment within 1 h of presentation.[21] However, patients with SCD have been shown to have a 70-min increase in wait time compared to the goal set by the APS.[28] As such, bias toward patients with SCD results in significant undertreatment of pain as well as missed diagnoses.[22, 29]

Patients with SCD utilize opioid medications to treat acute and chronic pain. The opioid epidemic has complicated this, as an effort was made to limit the use of opioids and overprescribing.[30, 31] With the rise of the opioid epidemic, patients with SCD are frequently accused of opioid misuse by healthcare workers, which leads to insufficient analgesic care.[27, 32] However, when looking at opioid-related deaths due to overdose between 1999 and 2013, only 0.05% occurred in patients with SCD. Additionally, the percentage of opioid-related death is over five times higher in patients with chronic pain conditions such as fibromyalgia and migraines compared to patients with SCD.[32]

Clinicians also overestimate the prevalence of addiction among patients with SCD. Contrary to this belief, most patients with SCD take less than 50 daily oral morphine milligram equivalent (OME).[33–35] The median OME dose was 6.1 in patients with SCD, with 71% of patients using less than 10 OME daily.[34] Estimates show that 55–87% of patients use only 0–5 OME daily.[35] While there is no OME level without risk, taking less than 5–10 OME daily does not greatly increase the risk of accidental overdose if taken as prescribed. The risk of overdose greatly increases when daily doses are greater than 50 OME.[36] Despite this, patients with SCD are perceived as being at greater risk of developing opioid use disorder and having an opioid-related death.[27]

STIGMA

Disparities in care are further exacerbated by different forms of stigma, which we define as a negative perception of an individual based on a real or perceived characteristic, such as a condition like SCD. Stigma can be further stratified into other categories that include social, self, and health professional stigma.[37] Social stigma occurs in relationships where patients with SCD may feel that others (their peers, employers, educators) view them negatively due to pain, hospitalizations, and subsequent loss of employment/school time.[37, 38] These aspects of social stigma carry over into societal stigma against patients with SCD, which involves the structures and policies that regulate where a patient might seek employment, education, or healthcare.[37] Self-stigma represents negative internalized feelings about one's worth and capabilities, and patients with SCD have been shown to have negative self-evaluations in surveys.[39] Given that the incidences of anxiety and depression are high among patients with SCD, these comorbidities may contribute to self-stigma as well.[40, 41]

Health professional stigma is a subtype of social stigma, such as providers who use harmful language regarding patients with SCD and/or deliver substandard care. The language used by providers to describe patients with SCD has included "over-reporting of pain," "drug-seeking behavior," or "caring for patients with SCD is frustrating."[42–46] Healthcare providers have been shown to under-prescribe opioid analgesics as well as non-analgesic SCD therapies, such as hydroxyurea, prophylactic antibiotics, and preventative care.[47, 48] A contributing factor to this may be the negative provider and care team attitudes toward patients and the perceived overuse of opioid medications.[43–45]

RESEARCH AND ACCESS TO CARE

The treatment of patients with SCD has long been underresearched and underfunded.[49, 50] When measured in terms of NIH grants, researchers have found over three times as many grants for more publicized diseases, such as cystic fibrosis (CF, prevalence 30,000), compared to SCD (prevalence 100,000).[51, 52] In 2004, despite the differences in prevalence, $90 million in funding from the NIH was set aside for SCD research, while $128 million went to fund CF research. In 2018, though SCD prevalence in the US had increased while the prevalence of CF remained the same; NIH funding for SCD decreased to $76.3 million.[50]

SCD generates less funding for care and research as compared to CF and other rare diseases due to systemic racism.[50, 53] The CF community has a greater proportion of White wealthy advocates who fundraise and draw attention to CF research, which inspires other donors to contribute and creates a positive cycle that is not seen in the SCD community due to stigma.[37, 49, 53] Beyond research, patient access to SCD clinical care is limited compared to other rare diseases.[54] There are more than 140 hemophilia centers, compared to 77 total whole lifespan, pediatric, or adult SCD centers despite hemophilia affecting about half as many people in the US.[55, 56] SCD centers are scarce in low-income and rural communities. Finally, many patients with SCD suffer from limitations in health insurance. Patients with SCD on public aid such as Medicaid have been shown to endure worse outcomes.[57–59]

FUTURE WORK

Despite historical failures and present-day barriers to studying and treating SCD, there are ongoing national efforts to improve care. The American Society of Hematology (ASH) has focused on clinician education and published clinical practice guidelines for the management of complications relating to SCD: cardiopulmonary and kidney disease, transfusion support, cerebrovascular disease, management of acute and chronic pain, and stem cell transplantation. ASH has led workshops to enhance SCD knowledge and skills for generalists, such as analgesia, detection of sepsis, and management of ACS. The SCD Research Collaborative was created by ASH and hosts a centralized clinical data platform and Clinical Trials Network.[60]

Legislative advocacy has been a challenge in the past, with the two most important advances being the National Sickle Cell Anemia Control Act of 1972 (PL 92-294) and the Sickle Cell Disease and Other Heritable Blood Disorder Research, Surveillance, Prevention, and Treatment Act of 2018 (PL 115-327). Recently, a bill was introduced in Congress (H.R. 1672/S. 904) that focuses on improving access to comprehensive outpatient care for patients with SCD, ensuring access to mental health and ancillary services to meet needs, and federal funding for participating states. Although the bill has yet to be passed, its introduction suggests a degree of political will and congressional allyship to support the SCD community.[61, 62]

Novel treatment options including gene therapy are promising for a cure, though trials are ongoing. These options represent a shift in treatment from symptom management to disease-modifying and curative therapy. Allogeneic hematopoietic stem cell transplant is the only established cure for SCD; however, this treatment is limited by a paucity of compatible donors and risk of complications.[63] Currently, many of the FDA-approved medications for SCD including hydroxyurea, L-glutamine, voxelotor, and crizanlizumab, are underutilized and could help patients improve their quality of life and longevity while we await further progress with novel therapies. This is in part due to the shortage of hematologists who can deliver this specialized care.[64] Creative approaches are needed to bridge this gap and improve access to FDA-approved SCD therapies, such as starting disease-modifying drugs during hospitalizations and using the inpatient encounter to address preventative care.[65]

Other approaches are needed to address the issues of racial bias and stigma that patients with SCD experience from healthcare professionals. One framework aims to address negative implicit biases, defined as unconsciously held beliefs toward a person or people, among residents regarding their care of patients with SCD by using cognitive behavioral therapy techniques.[46] Video interventions have been shown to improve the attitudes of providers.[42] Scholarly work that reframes the management of chronic SCD pain to acknowledge and address the neurologic, psychological, and social aspects is helping undo medical professional biases and discriminatory practice.[66] Addressing biases will help build understanding and can lead to higher quality of care.

CONCLUSION

SCD has a long history of being a neglected disease due to systemic racism in care, research, and funding. However, there is hope as we reach a new frontier in SCD care and research. We can continue to move forward by learning from missteps, addressing biases, listening, and pushing for change to usher in an era where patients with SCD may have access to equitable and compassionate care with a better quality of life.

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Declarations

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