

Psychiatric Issues in Adults with Sickle Cell Disease

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Psychediatric issues are common in sickle cell disease (SCD)¹ but have not received sufficient attention in the clinical or research literature. These issues are further complicated by the social, economic, and healthcare disparities experienced by many African Americans. This column reviews the following psychiatric issues in SCD, with particular focus on recent research: first, depression and anxiety resulting from living with a chronic stigmatizing disease associated with chronic pain, unpredictable painful crises, multiple serious complications, poor health-related quality of life (HRQOL), and high mortality; second, problems of pain management, frequent undertreatment, and potential for substance abuse and addiction; third, coping styles; fourth, alcohol abuse; and last, central nervous system (CNS) injury and resulting cognitive dysfunction from strokes, primarily during childhood.

OVERVIEW OF SICKLE CELL DISEASE

SCD is an autosomal recessive genetic disorder of hemoglobin (Hb) structure and the most common of the hemoglobinopathies. While it usually results in anemia, the primary symptomatic manifestation of SCD is pain. The most severe form of SCD, homozygous sickle cell anemia (Hb SS), occurs when Hb S is inherited from both parents. In the United States, this happens in approximately one in 375 African-American births. Other genetic variants producing SCD include two forms of sickle cell-beta thalassemia (Sβ⁰ and Sβ⁺) and sickle cell-hemoglobin C (SC). Individuals with sickle cell trait, ie, heterozygotes for Hb S, do not experience any adverse clinical consequences (except under acute hypoxic conditions, eg, exposure to high altitude without time to accommodate) and have had a selective advantage against malaria. Those with the homozygous disease face a chronic disease, with onset in childhood leading to devastating consequences.

SCD occurs primarily in those of African descent, but it also afflicts people of Mediterranean, Middle Eastern, and Asian origins. Approximately one in 300 African-Americans have SCD (>70,000 people) and 8% have sickle cell trait.

The consequences of SCD are aggravated by social, economic, and healthcare disparities. African Americans are on average poorer, have more limited access to healthcare services, and die sooner than Caucasians.² Medical advances, such as prophylactic penicillin for children, have transformed the disease from a pediatric illness with few surviving beyond adolescence into one chronically extending into adulthood. Life expectancy has increased from a mean of 14 years of age in the 1970s to close to 50 years of age at present.³ By the 1980s, the federally funded Cooperative Study of Sickle Cell Disease (CSSCD)⁴ found median survival was into the fourth decade for homozygous patients. Patients with doubly heterozygous forms of SCD, such as Hb SC, fared even better, and the presence of a higher percentage of persistent fetal hemoglobin (Hb F) was associated with less severe disease and greater longevity.

This improved survival has created the relatively new phenomenon of adults with chronic SCD. Consequently, much less is known about psychosocial factors in adults with SCD than in many other chronic medical disorders, with most studies to date addressing prevalence of depression (see below). The increase in longevity has also resulted in physicians for adults treating pain resulting from a disease for which they have lim-

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ited training and experience. In one inpatient study, one-third of patients reported inadequate pain relief and nearly 50% reported long delays in being treated for pain.⁵ The evidence base used to guide treatment for the growing population of adults with SCD has been very limited, with even less data regarding psychosomatic interactions, though both are now an active focus of investigators.

Most familiar to clinicians are the acute painful episodes known as “sickle cell crises,” thought to be due to acute vaso-occlusion by sickled red blood cells. Recurrent crises represent the most common reason patients seek acute medical care. Dehydration, temperature extremes, infection, changes in altitude, stress, and physical exertion may precipitate crises, but most crises occur without an identifiable cause. Vaso-occlusion causes acute pain in the short run and chronic pain and end-organ damage in the long run, potentially affecting all organ systems with particular harm to bones, kidneys, lungs, eyes, and brain. Complications include acute chest syndrome, avascular necrosis, priapism, ischemic leg ulcers, transient ischemic attacks and stroke, osteomyelitis, gallstones and cholecystitis, and renal insufficiency.

Clinicians and investigators have tended to focus on acute crisis pain and to equate crisis with acute healthcare utilization, ie, emergency room visits or hospitalization. However, the recent Pain in Sickle Cell Epidemiology Study (PiSCES)⁶⁻¹³ has demonstrated that pain in adults with SCD is far more prevalent and severe than previous studies have portrayed, and it is mostly managed at home.⁶ Therefore, it has been vastly underestimated when measured by using only healthcare utilization. In this prospective study, >50% of adults with SCD experienced pain, crises, or healthcare utilization on >50% of the days. Almost 33% experienced pain nearly every day, with the mean intensity in the middle range. In contrast, only approximately 15% rarely experienced pain. Crises and healthcare utilization were far less common than reported pain days; pain days that were not associated with a crisis occurred 10 times more often as pain days associated with healthcare utilization. Thus, contrary to commonly held belief, pain in adults with SCD is the rule rather than the exception. Since SCD adults infrequently utilize health care even in response to severe pain, there is a vast, mostly submerged iceberg of sickle cell pain that is managed outside of medical facilities and not seen by most professionals.

Smaller longitudinal studies measuring daily pain in children have also found that pain was most often managed at home rather than within healthcare facilities.⁷ How might this be explained? Behavioral theories suggest that many factors, besides pain itself, influence the response to pain.⁷ Adults with SCD carefully weigh the decision to come to a busy emergen-

cy department for treatment of even severe pain, where they may face long waits, stigmatization, and labeling as “drug-seeking.” Some manage their pain at home because of barriers in accessing health care, especially finding clinicians with SCD expertise, competing life priorities (eg, no child care), and lack of transportation. Evidence of each of these may be found in behavioral studies of SCD.⁷

HRQOL in adults with SCD is significantly worse than national norms.⁸ Adults with SCD have quality of life (QOL) that is similar to dialysis patients and poorer than adults with cystic fibrosis (except for mental health). Not surprisingly, QOL in adults with SCD significantly decreases as pain levels increase.

DEPRESSION AND ANXIETY

As with most chronic diseases, depression and other psychiatric disorders are common in SCD.¹³⁻¹⁵ Rates of depression are similar to those found in other serious chronic medical disorders, ranging from 18% to 44%,¹⁶⁻¹⁸ and are increased over rates in the general population even when one controls for illness-related physical symptoms.¹⁹ In a Nigerian study, subjects with SCD had a prevalence rate of depression greater than those with cancer or malaria (but less than those with HIV/AIDS).²⁰ While studies of depression in children with SCD have shown mixed results, children experience high rates of fatigue and other somatic complaints, impaired self-esteem, feelings of hopelessness in the context of frequent hospitalizations, absences from school, and the inability to experience a normal childhood.¹

There are many potential contributing causes to symptoms of depression and anxiety in SCD. These include the chronicity of the illness; unpredictability of crises; chronic pain; overwhelming nature of medical complications, including anemia, fatigue, growth retardation, physical deformities, leg ulcers, renal failure, strokes, and substantially reduced life expectancy; and racial prejudice and stereotyping. SCD may result in social derision, disability, and financial stress²¹ as well as stigmatization for pseudoaddiction to opioid analgesics.²² One study found that adults with SCD had lower self-esteem than those with HIV/AIDS or cancer.²⁰ Chronically prescribed opioids may contribute a component of substance-induced mood disorder.¹⁵

Children with SCD are often underweight, shorter than normal children, and have delayed puberty. With their small stature, adolescents with SCD encounter problems with self esteem, dissatisfaction with body image, and social isolation, with participation in athletics also limited due to fear of

initiating a vaso-occlusive crisis.¹ School performance suffers when hospitalizations lead to missing multiple school days. Accordingly, adolescents often experience hopelessness and social withdrawal.²³

PiSCES found that 27.6% of adults with SCD were depressed and 6.5% had an anxiety disorder.¹³ Depressed subjects had pain on significantly more days than nondepressed subjects (mean pain days=71.1% versus 49.6%, $P<.001$). On non-crisis days, depressed subjects had higher mean pain, distress from pain, and interference from pain than those without depression. Both depressed and anxious subjects had poorer functioning on all dimensions of HRQOL, even after controlling for demographics, hemoglobin type, and pain. The anxious subjects had more pain, distress from pain, and interference from pain, both on non-crisis days and on crisis days, and used opioids more often. Anxious patients were also more likely to be emergency room “frequent flyers.”

CHRONIC AND ACUTE PAIN AND OPIOID USE

As noted above, recurrent painful crises represent the most common reason patients with SCD seek acute medical care. Painful crises most frequently involve the abdomen, chest, back, and extremities. The average adult patient experiences <1 vaso-occlusive crisis per year for which he or she seeks medical care, but a very small fraction (approximately 1%) do so several times per year.²⁴ However, the PiSCES found that most self-defined painful crises do not result in acute healthcare visits.⁶ Both the unpredictability and the severity of crisis pain contribute to its psychological morbidity and debilitation. It is interesting that higher hematocrit is associated with more pain. Contrary to many studies of acute and chronic pain of other causes, men and women with SCD report generally similar pain experiences, both in terms of acute crisis pain and chronic pain, as well as HRQOL.^{8,9}

Opioid analgesics are the mainstay of therapy for acute pain crises in SCD. Therefore, by adulthood, most patients have had many years of intermittent exposure to opioids. Opioids help control pain, improve functional capacity, and decrease hospitalizations in patients with SCD.²⁵ Chronic opioid use often results in tolerance and physiologic dependence, but much less often abuse and addiction. Opioid abuse and addiction behaviors can be difficult to define when prescribed for chronic pain. While there is little evidence in the medical literature that suggests addiction is frequent in SCD, physicians and other healthcare providers routinely overestimate its risk and prevalence.²⁶ Over 60% of nurses believe addiction

is prevalent in SCD,²⁷ and >50% of emergency department physicians and 25% of hematologists thought that >20% of SCD patients are addicted.²⁸ Some of this distorted perception results from failure to distinguish between physiologic tolerance and dependence versus addictive behaviors.²²

Because of their fear of causing or exacerbating addiction, physicians may under-treat pain in patients with SCD.²⁹ This may result in pseudoaddiction, where addiction-like behaviors occur as a result of inadequate pain management.³⁰ An example mislabeled as “drug-seeking behavior” occurs when a patient with acute crisis pain asks for a higher dose of opioid than he has been given because the physician has failed to increase normal dosage in recognition of tolerance developed through chronic opioid therapy.²² Opioid abuse and addiction can occur in adults with SCD; some patients may inappropriately use opioids for non-pain symptoms such as insomnia, depression, and anxiety. It should be noted, however, that opioids do not have any specific adverse effects on SCD. In contrast, cocaine is very harmful since in causing small vessel spasm it may precipitate or escalate sickling, and it increases the already elevated risk of stroke and other ischemic events.³¹ One form of opioid misuse in SCD to be aware of is the barter exchange of prescribed opioids for cocaine. This possibility should always be considered whenever a urine toxicology screen is negative for opioids in a SCD patient who says he has been taking his analgesic as prescribed.

COPING STYLE

Numerous studies have examined the influence of coping style in SCD, specifically how negative thinking and passive adherence contribute to increases in pain perception, opioid use, and healthcare utilization.¹¹ “Negative thinking” is a cognitive set composed of catastrophizing and self-statements of fear and anger, in which catastrophizing has seemed the most important component in pain research. “Catastrophizing” refers to an exaggerated negative orientation or “mental set” toward pain stimuli and pain experience. Individuals who catastrophize may develop beliefs with a high degree of aversion to pain-eliciting situations, pay more attention to their pain sensations, and consume more opioids.³² Catastrophizing can be understood as a set that includes rumination, magnification, and helplessness to deal with pain. Although it has been identified as an important factor affecting outcomes in several painful conditions, it appears that the role of catastrophizing in other conditions cannot be generalized to SCD. While adults with SCD have higher mean catastrophizing scores than found in studies of other chronic pain conditions that

are not lifelong and life-threatening, no differences were found between higher and lower catastrophizers in intensity of pain, distress, interference, opioid use, or healthcare utilization.¹¹

ALCOHOL ABUSE

Alcohol abuse is common in patients with chronic pain and painful medical disorders, but until recently it had not been studied in SCD. In the prospective PiSCES cohort, almost one-third of SCD adults were abusing alcohol.¹⁰ There were no significant differences between alcohol abusers and nonabusers on demographics, biologic variables, depression, anxiety, or measures of pain and crisis. Alcohol abusers did not use opioids any more often, but THEY reported more pain relief from opioids than did nonabusers. Alcohol abusers had fewer unscheduled clinic visits, emergency room visits, hospital days, and any healthcare utilization for SCD; however, this was only statistically significant for emergency room visits. Surprisingly, QOL was similar between both groups, except that alcohol abusers unexpectedly had better overall physical QOL. Alcohol abusers were more likely to report coping by ignoring pain, diverting attention, and using particular self statements.

PSYCHOSOCIAL INTERVENTIONS

There have only been a few small short-term biobehavioral intervention trials that have attempted to alter pain and healthcare utilization in SCD. A multidimensional, intense intervention to improve pain management of SCD patients through counseling and carefully monitored opioid prescribing reduced emergency department visits and hospital admissions.³³

In another trial,³⁴ a pain-coping skills intervention in adults with SCD lowered pain perceptions from a laboratory-induced pain stimulus and significantly increased coping attempts. On pain days when subjects used coping strategies, they had fewer healthcare contacts than on pain days when they did not use coping strategies. Other interventions have met with limited success. A brief training in cognitive coping skills resulted in increased coping attempts, decreased negative thinking, and lower tendency to report pain during laboratory-induced noxious stimulation.³⁵ A family intervention in children met with some success.³⁶ Self hypnosis as an adjunct to traditional treatment improved sleep, reduced pain days, and reduced the use of pain medications.³⁷ There are no published randomized controlled trials of antidepressants in patients with SCD.

CENTRAL NERVOUS SYSTEM INJURY

Brain disease from SCD complications may begin early in life. Children with SCD may experience a wide variety of neurologic syndromes, including ischemic and hemorrhagic stroke, transient ischemic attacks, "soft neurologic signs," seizures, headache, coma, visual loss, altered mental status, cognitive difficulties, and covert or "silent" infarction. Approximately 25% to 33% of affected children have CNS consequences of SCD.³⁸ Seizures occur in 12% to 14%.^{39,40} Once very common in children with SCD, the incidence of stroke has been reduced through chronic transfusion and other interventions.⁴¹ Intellectual deficits, including borderline-to-moderate mental retardation and reduced language function, have been reported.⁴² Not surprisingly, cognitive deficits in children with SCD lead to educational and social problems, and even dementia later in life.⁴³ Acquired neurologic impairments in children with SCD are associated with difficulties in the decoding of emotions of other children and adults.⁴⁴ A small, nonrandomized study⁴⁵ suggests that hydroxyurea therapy may improve cognitive functioning in SCD. *PP*

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