Comorbid depression in sickle cell disease: An overview of determinants and need for early detection

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Abstract

Sickle cell disease (SCD) is a chronic illness, characterized by periods of painful crises, frequent hospitalizations, and multiorgan dysfunction; patients are frequently exposed to diverse psychological stressors and insults which adversely impact on overall quality of life (QOL) and survival. The following key words: "sickle cell disease," "psychological dysfunction,", "psychopathology," "co-morbid depression," "quality of life," "disease severity," "treatment," and "clinical outcome" were used for literature search on PubMed, PubMed Central, Google Scholar, African Index Medicus, and Scopus database sources. No limitation as to the year of publication was applied and the oldest paper retrieved was published in 1989. The search was restricted to depression occurring in the background of SCD and publications in English language. The studies retrieved dealt mainly on the epidemiology, etiopathogenesis, and treatment of co-morbid depression in SCD, whereas papers dealing primarily with depression not related to SCD were rejected. All papers identified were assessed by the authors with a view to highlighting the prevalence and effect of depression on the clinical course of SCD. Comorbid depression was shown to constitute a significant burden in subjects living with SCD; the prevalence of which increases with increasing disease severity. In affected SCD patients, it has adverse effects on QOL and disease course. The need for early detection of comorbid depression in patients with SCD is hereby emphasized, with a view to instituting appropriate treatment geared toward ameliorating its adverse effect on disease morbidity.

Key words: Psychopathology, quality of life, sickle bone pain crises, sickle cell disease

INTRODUCTION

Sickle cell disease (SCD) is a chronic multisystem disorder characterized by a single point substitution in the beta hemoglobin gene. It is one of the most common genetic disorders globally, having high prevalence rates in Africa, Middle East, Asia, and parts of America, (particularly among the African-American subpopulation).[1-3] The hallmark of the disease includes red cell sickling under conditions of reduced oxygen tension, with resultant ischemia, vascular dysfunction, and end-organ damage.[4,5] The term SCD encompasses the homozygous (hemoglobin SS [HbSS]) and other double heterozygous hemoglobin phenotypes such as hemoglobin S plus C (HbSC), hemoglobin S plus D (HbSD), hemoglobin S plus

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E (HbSE), and beta thalassemia (HbS/β-thalassemia).[6] The clinical severity of SCD ranges from milder disease phenotypes in HbSC, HbSD, and HbSE diseases to more severe manifestations in HbSS and HS/β-thalassaemia, with poorer disease outcome.[7]

The homozygous HbSS is associated with severe disease presentation, and it is the most common variant in Nigeria and parts of West Africa.[8] Clinically, patients present with recurrent acute manifestations known as "crises" which is interspersed with periods of apparent normalcy, known as steady states.[9] Recurrent acute and chronic pain form part of the clinical spectrum of disease, while the former (known commonly as vaso-occlusive crisis) is typical of the crises of SCD, the latter (including avascular necrosis, commonly of the hip and shoulder joints) represents a long-term disease complication. These have been reported to have a negative impact on the quality of life (QOL) of affected individuals, often associated with depression, disability, unemployment, and opioid analgesics dependence.[10,11]

SCD is associated with high disease-related mortality arising mainly from complications of severe anemia and end-organ dysfunction. These are particularly marked in Sub-Saharan Africa, where up 90% of affected children have been estimated to die before the age of 5 years, in the absence of intervention.[12,13] Following the turn of the century, however, significant improvement has been witnessed in the management of SCD patients which has translated into improved survival and longevity, particularly in countries with better health indices. Indeed the introduction of some novel therapeutic interventions such as hydroxycarbamide and stem cell transplantation (SCT) have revolutionized the treatment of individuals with this disorder; SCT has even been associated with cure in some series.[14-16] With increased survival observed in SCD patients following the introduction of these novel treatment modalities, the presence of long-term disease complications has been brought to the fore; these were hitherto less frequently encountered due to high disease-related mortality. Sickle-related psychopathology (which prominently includes comorbid depression) is among the long-term complications which are increasingly reported; however, due to its rather latent nature, the diagnosis could be missed by the unsuspecting clinician.

METHODOLOGY OF RELEVANT DATA RETRIEVAL

The literature search for this review was based on PubMed, PubMed Central, Google Scholar, African Index Medicus, and Scopus database sources; no limitation as to the year of publication was applied. The oldest paper retrieved was published in 1989. The following keywords were used in the search: "sickle cell disease," "psychological dysfunction," "psychopathology," "co-morbid depression," "quality of life," "disease severity," "treatment," and "clinical outcome."

The search was restricted to depression occurring in the background of SCD, publications in English language, and was conducted in the month of January 2017.

The studies retrieved dealt mainly on the epidemiology, etiopathogenesis, and treatment of comobid depression in SCD, whereas papers dealing primarily with depression not related to SCD were rejected.

All papers identified were assessed by the authors and subsequently retained or rejected based on the above criteria.

The information from these publications is discussed in this review, with a view to highlighting the magnitude of comorbid depression in SCD as well as to emphasize the need for its early recognition and management by health professionals who care for patients with this disorder.

DISEASE CHRONICITY AND SEVERITY AND THE DEVELOPMENT OF COMORBID DEPRESSION IN SICKLE CELL DISEASE

Diseases that run a chronic course have been associated with significant psychological burden arising mainly from frequent hospitalizations, the cost of repeated investigations, and treatment with the attendant drain on family finances [Figure 1].[17,18] SCD follows a chronic and often "drawn-out" clinical course, characterized
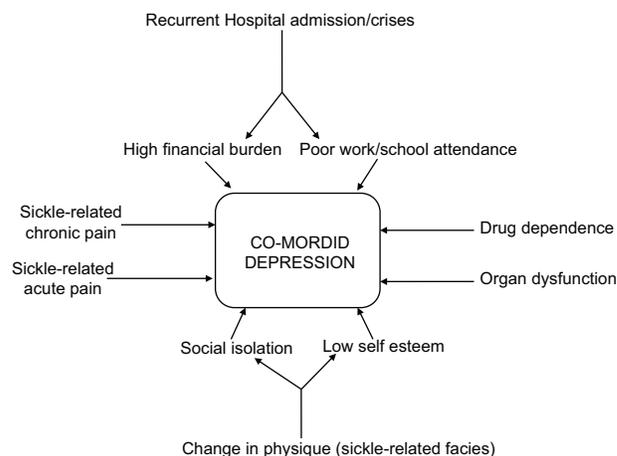

Figure 1: Determinants of depression in sickle cell disease

by crises, interspersed with periods of steady clinical conditions. The crises periods are times of significant morbidity in patients and are commonly heralded by acute exacerbations in symptoms which could manifest as acute painful (vaso-oclussive crisis), sequestration, aplastic, and the so-called hyperhemolytic crises [Figure 2].[19] These are commonly precipitated by "triggers" which are related to a myriad of causes such as infection, physical and emotional exertion, dehydration, acidosis, and exposure to extremes of temperatures.[20,21] In the presence of appropriate "triggers," intravascular red cell sickling occurs leading to deformation of the red cell and change in shape to the characteristic sickle cells. Sickle red cells adhere to one another, to platelets, white cells, and the endothelial lining, resulting in vascular occlusion, ischemia, and pain.[22,23] The resulting reduction in blood flow from vascular occlusion induces more red cell sickling, thus setting up a vicious cycle of increasing red cell sickling, vaso-occlusion with resultant endothelial, and other organ/system dysfunction.

In the light of the above, it is important to emphasize that the overall burden of SCD, including multiple end-organ dysfunction, changes in physique and psyche, with attendant psychological dysfunction could be traced to the frequency and severity of sickle-related crises. In recognition of this, the goal of management of patients with SCD is, therefore, geared toward shortening the periods of crises and prolonging the steady state periods as much as possible, through diverse interventions.[24,25] Other sickle-related crises, such as aplastic, hyperhemolytic, and organ sequestration characteristically cause anemia which could lead to hospitalization and blood transfusion, to correct symptomatic anemia [Figure 2]. Recurrent anemia (with acute exacerbations which could occur in sickle-related hyper-hemolysis) is associated with poorer QOL and clinical outcome and has equally been shown to underlie a number of sickle-related complications such as skeletal abnormalities and organ failure [Figure 2].[26] On account of this, it is thus important that anemia is recognized in SCD patients and decision as per red cell transfusion taken early to reduce morbidity and mortality. Even though red cell transfusion (particularly exchange blood transfusions) could significantly improve anemia, reduce complications. and impact positively on wellbeing, complications ranging from alloimmunization, transfusion-related acute lung injury, increased risk of acquiring transfusion transmissible infections (TTIs), and iron overload could occur.[27-31] Iron overload is a recognized cause of significant morbidity in SCD patients who have transfusion-dependent anemia, arising from iron deposition and organ damage, especially cardiac, hepatic, and endocrine.[32-34] Failure of any of these organs could significantly impact on the general well-being and QOL and could be a prelude to the development or exacerbation of a frank depressive illness or other psychopathology in SCD participants [Figure 2]. The general prevalence of TTIs in SCD patient tends to parallel the degree of application of safe blood transfusion practices and increases the overall disease burden, particularly in
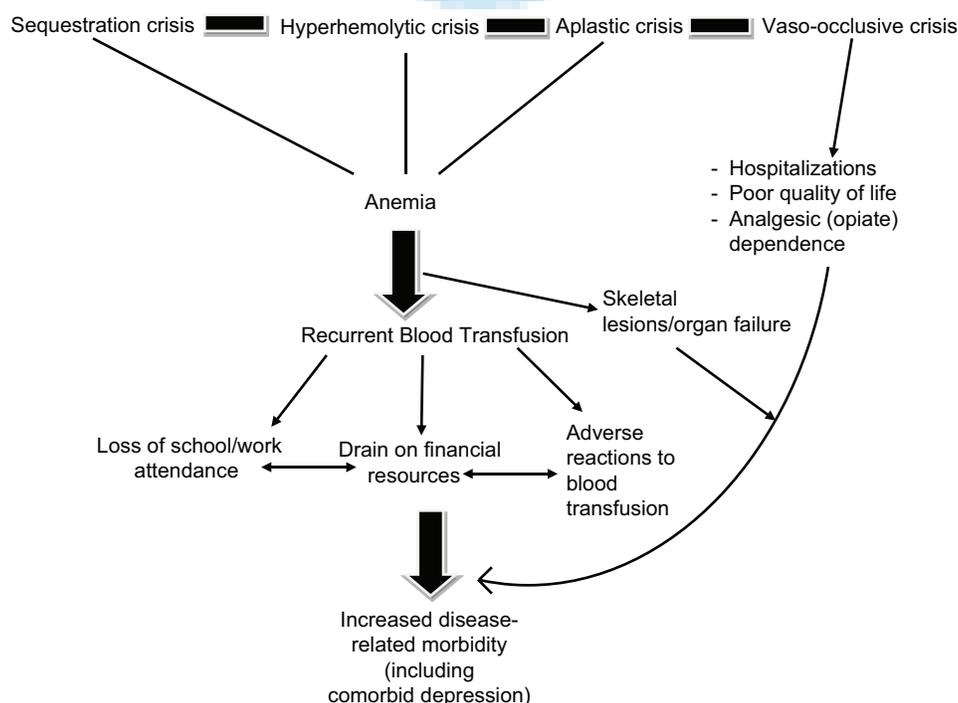

Figure 2: Sickle related crises and comorbid depression

resource-poor settings. Studies in parts of Nigeria and Togo have confirmed that SCD patients on regular blood transfusion could be prone to acquiring TTIs.[35,36] Infection with any of the TTIs (particularly the hepatotropic viruses) could remarkable increase the hepatopathy of SCD, with a significant increase in disease burden and risk of depression. It is thus evident from the foregoing that the chronic and often debilitating nature of the SCD, which has recurrent acute and chronic pain, increased risk of organ dysfunction, drug dependence, and family and financial stressors as some of its hallmarks, clearly makes a perfect "breeding ground" for the development of comorbid depressive disorder.

THE EPIDEMIOLOGY OF COMORBID DEPRESSION IN SUBJECTS WITH SICKLE CELL DISEASE

Comorbid depression in subjects living with SCD is frequently not identified or even misdiagnosed by health-care professionals that are routinely charged with the responsibility of managing individuals with this disorder.[37] In this unrecognized state, comorbid depression may only become apparent when significant loss of routine ability and function have occurred in these subjects, a situation that significantly increases both the cost of care and the time to full recovery.[38]

The reported rates of co-depression in SCD subjects are generally comparable to that reported for other chronic medical disorders and ranges from 18% to 44% but are significantly increased when compared to the general population prevalence (even after controlling for illness-related physical symptoms).[10,39,40] Previous study among Nigerian subjects with SCD showed a higher prevalence rate of depression than in patients with cancer or malaria but lower than those with HIV/AIDS.[41] The prevalence of comorbid depression has equally been found to be higher in children and adolescents, mainly because children experience high rates of fatigue and other somatic complaints, tend to have more impaired self-esteem and feelings of hopelessness, occasioned by frequent hospitalizations, absences from school, and the inability to experience a normal childhood.[42]

A number of other studies have equally shown that African-American adults experienced higher prevalence rate of SCD-related depressive illness than do the general population (26% vs. 9.5%, respectively).[43,44] Similarly, the higher prevalence rate of other forms of psychosocial dysfunction in adolescent population with SCD including problems in social relationships, isolation, and school failure have been reported; 29% of participants with these satisfied the criteria for the diagnosis of depression,

using the symptom scales.[45] In a study of 440 adult SCD patients, 43% showed depressive symptoms, whereas in another study, 63% (of 38 participants) showed positive psychiatric morbidity, comprising mixed anxiety and depressive symptoms.[46,47]

Jerrell et al. reported depression prevalence of 46% in SCD patients (90% of which had dysthymia, whereas 10% was diagnosed with major depression) and was associated with adverse course and outcomes.[48] The study equally emphasized the need for early and sustained treatment of comorbid depression in patients with SCD, either by the primary care providers or psychiatrists with a view to reducing the chronic, severe pain-depression cycle.[48]

THE DEPRESSION-PAIN CYCLE

Over the years, the goal of management of diseases that follow a chronic clinical pattern had involved appropriate and adequate symptom management in such a way as to maintain an acceptable QOL.[49,50] The QOL is very important as it is related to the general outlook of the patient which in turns hinges on the desire to live (to survive). The desire to live is needed in patients with chronic diseases as it guarantees patients' cooperation and active participation in decision-making and treatment.

Sickle-related acute and chronic pains are important symptom complexes of variable duration and intensity experienced by patients and have been shown to have significant adverse impact on QOL and mortality.[51] It has been documented that depression not only commonly complicates chronic pain but also could significantly lower the threshold for tolerance of pain as well as the ability to cope with it.[52] Persistent chronic pain in individuals with SCD may equally induce withdrawal from interpersonal contacts and consequent self-absorption.[52] A withdrawn, self-absorbed patient is more likely to show negative health-seeking behaviors and other activities that could impact adversely on clinical disease severity such as abstinence from follow-up clinic visits as well as discontinuation of the use of prescribed routine medications. In addition, the SCD patient with recurrent pain may exhibit anger and resentment and increased predisposition to opiate use and dependence, particularly when treatment is perceived to be delayed or denied.[52] An earlier study emphasized this observation by reporting that pain severity was correlated with depressed mood, hopelessness, anger, and shame in SCD patients who experience frequent bone pain crises.[53] Ironically, dependence on opiate and other analgesic drug has been shown to induce depression, especially following prolonged usage [Figure 1].[52]

The acute painful crisis of SCD has been attributed to be a common cause of frequent emergency room visits and hospitalizations, absence from school and work, loss of revenue, and increase in other disease-associated stressors to both patient and family.[54-56] The influence of sickle bone pain crises on disease morbidity has been widely emphasized in a number of reports where these have been consistently linked with adverse prognosis and poor outcome.[57]

Correspondingly, an American study had reiterated that frequent pain crises were significantly associated with depression, somatization, and more frequent hospitalizations.[58] Against the backdrop of this "unholy alliance" between sickle-related pain and reduced physical functioning and subsequently comorbid depression, it is very important that the cycle of pain is truncated in SCD patients to reduce its adverse impact on QOL. This is even made more imperative by the observation that poorly managed acute and chronic pains of SCD could lead to poor coping strategies, which could predispose to higher frequency of vaso-occlusive pain, opioid analgesic dependence, increased emergency room visits and hospital admissions, increased sickle-related complications, poorer physical function, and further reduction in the QOL.[59,60] The management of sickle-related pains should include interventions for acute pain as well as management aimed at addressing chronic pain and its sequelae. Aside from specific interventions which include different forms of analgesia, other modalities for addressing pain in SCD include the use of complementary and alternative medicine such as prayers to improve coping and well-being.[61-63] Indeed an increasing number of studies in SCD populations have revealed that prayer and a belief in God are important coping strategies that could be applied in patients with significant benefits.[64-67]

Due to a combination of chronic anemia, frequent stroke (including silent infarcts), and recurrent bone pain crises, SCD patients tend to have delayed growth and development, which typically manifests as the so-called SCD facie (lower body weight, bony deformities, and an asthenic stature), cognitive impairment/delays, delayed puberty, and missed school days.[68,69] These complications get reenforced by the period of adolescence and could present as feelings of inadequacy, lower self-esteem, social isolation, poor school performance, and general hopelessness.[70,71] In extreme cases, suicidal thoughts have been observed; indeed rates of successful suicides are reported to be higher in SCD patients, compared to other patients with chronic diseases.[72]

POSSIBLE LINES OF PHARMACOLOGICAL INTERVENTIONS FOR COMORBID DEPRESSION IN SICKLE CELL DISEASE

In general, psychological dysfunction in patients with SCD, including major depression, has been successfully treated with a number of modalities which include the use of antidepressants and other interventions aimed at improving the QOL and ameliorating disease course.[10,73] It will, however, appear that there is suboptimal treatment uptake for SCD patients with depression, arising mainly from low recognition (low index of suspicion) by physicians.[73] Barakat et al. reported that only one-third of patients with SCD reported receiving treatment for depression from a mental health professional.[62] Traditionally, affected individuals are commonly offered any of the tricyclic antidepressants (such as amitriptyline, doxepin, and imipramine) [Table 1]. However, with the turn of the century, newer antidepressants (such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and heterocyclic second-generation agents) are becoming more popular among clinicians [Table 1].[63] These new generation antidepressants have been observed to be safer and more user-friendly, with attendant better compliance, compared to the traditional agents.[63] Drawing from the observation that combining antidepressants with opioid analgesics is significantly associated with fewer hospital visits as a result of sickle-related vaso-occlusive pain,[74] careful combination of these two drugs may actually be indicated in a properly selected group of patients. The use of antidepressants for comorbid depression may be associated with drug-related adverse effects such as bleeding and bone marrow suppression.[43] It is important that physicians and caregivers are mindful of the possibility of these adverse effects since they could become exaggerated in SCD patients that are

Table 1: Treatment of depression in sickle cell disease

Nonspecific (nondrug) treatment	Specific (drug) treatment
CAM, including prayer and belief in God	Tricyclic antidepressants, TCADs (such as amitriptyline, doxepin, and imipramine)
Psychological interventions including cognitive-behavioral therapy, special educational support, etc.	SSRIs
Improvement in general well-being	SNRIs
	Heterocyclic second-generation antidepressants

CAM: Complementary and alternative medicine, SSRIs: Selective serotonin reuptake inhibitors, SNRIs: Serotonin-norepinephrine reuptake inhibitors, TCADs: Tricyclic antidepressant drugs

concomitantly on nonsteroidal anti-inflammatory drugs and hydroxycarbamide, respectively.

It is equally very important to observe that drug treatment alone does not completely address the spectrum of depressive disorders in these patients; therefore, psychological interventions including patient education, cognitive-behavioral therapy, and special educational support have been found to significantly improve the QOL and should be given in combination with drug therapy [Table 1].[75] In practice, however, it will appear that these important aspects of therapy for SCD are usually ignored by caregivers and therefore not readily made available to patients that need it, leading to poor performance status and clinical outcome.[62]

CONCLUSION

Comorbid depression appears to be largely unrecognized, undertreated, and underreported; this situation is likely to exaggerate in parts of Sub-Saharan Africa, with its health infrastructural deficits and dearth of qualified specialist health-care providers. The above state of affairs may, therefore, constitute a "perpetuating factor" for recurrence of chronic, debilitating bone crises in patients with its attendant effect in engendering a worse disease course, poor school performance, low self-esteem, and overall poorer QOL and individual productivity. Fortunately, it has been widely reported that the use of antidepressants for adjuvant pain relief in SCD is associated with remarkable improvement in comorbid depression, arising from recurrent sickle-related bone pains.

The above analysis has emphasized the need to increase the awareness, assessment, and surveillance of depressive symptoms by all health-care providers involved in the management of patients living with SCD. Early recognition and optimal treatment of comorbid depression are expected to significantly impact on clinical outcome and overall survival in individuals affected by this disorder, particularly those with more severe clinical phenotype.

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Conflicts of interest
There are no conflicts of interest.

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