# Psychopathology in Sickle Cell Disease

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**Summary**

**Acute and chronic medical conditions are often complicated by psychiatric symptoms. Depression and anxiety are two of the most common psychiatric symptoms that complicate the diagnosis and management of medical conditions. Despite the well-known association between chronic medical conditions and psychiatric diagnoses, psychopathology among individuals with Sickle cell disease (SCD) is not well recognised. The purpose of this article is to examine the relationship between psychiatric symptoms and SCD. We reviewed the existing literature regarding the psychological sequelae among patients with SCD. We then recommend how to better identify and treat psychopathology associated with this condition.**

**Keywords:** ***Sickle cell disease, Psychopathology, Depression, Anxiety, Psychosis, Posttraumatic stress disorder PTSD***

**Résumé**

Des conditions médicales intenses et chroniques sont souvent compliquées par des symptômes psychiatrique. L'état dépresif, et l'anxiété sont deux des symptômes psychiatriques les plus fréquents que compliquent le diagnostic et la prise en charge des conditions médicales.

En dépit de l'association bien connue entre les conditions médicales chroniques et les diagnostics psychiatriques, psycopathologie chez des individus atteints de la maladie de la drépanocytose (SCD) n'est pas très bien reconnue. L'objet de cette recherché est d' étudier des rapports entre des symptômes pschiatrique et le SCD. Nous fait le bilan de la litérature actuelle pour ce qui est de la sequelae psychologique chez des patients attients de SCD.

Ensuite nous recommandons comment mieux identifier et soigner la psychopathologie associée avec cette condition.

## Introduction

Acute and chronic medical conditions are often compl.cated by psychiatric symptoms. Depression and anxiety are two of the most common psychiatric symptoms that complicate the diagnosis and management of medical illness. The incidence of major depressive disorder among the general population has been estimated between 5% and 8%. The incidence of depression may exceed 50% among patients with cerebrovascular accidents, and it is about 26% among patients undergoing coronary angiography.

Furthermore, 19-33% of patients with diabetes mellitus have been diagnosed with depression.[1] Despite the well-known association between chronic medical conditions and psychiatric diagnoses, psychopathology among individuals with SCD is not well recognized.[2] In this manuscript, we examine the relationship between psychiatric symptoms and SCD, and suggest how to promptly recognise these symptoms and treat them appropriately.

### *SCD*

SCD includes sickle cell anemia (HbSS), Sickle cell hemoglobin C disease (HbSC) and sickle cell b thalassemia. These conditions are genetic disorders of the blood that most often affect people of African, Middle Eastern, Mediterranean and Asian descent. Approximately one out of 600 African-Americans has SCD. In Nigeria, sickle cell anemia occurs at a prevalence of 2% and sickle cell haemoglobin disease occurs in 0.7% of the population.[3] SCDs are inherited in autosomal recessive pattern, whereby an individual requires two copies of the defected gene in order for the disease to become evident. In an individual that is homozygous for the sickle gene, almost all the hemoglobin in the erythrocyte is hemoglobin S.[4] In heterozygous carriers of the sickle cell trait, less than 50% of the hemoglobin is hemoglobin S. These individuals do not usually suffer from anemia or other severe complications of SCD, but approximately 5% of carriers develop benign hematuria. Unlike normal hemoglobin, A, hemoglobin S has a tendency to polymerize when the oxygen supply is reduced. The rate at which hemoglobin S forms polymers is dependent on its concentration in the erythrocyte; this is why individuals with homozygote genes have a higher tendency to form polymers when compared with individuals with heterozygous genes. As a result of polymerization, the erythrocytes take on a rigid or "sickle" shape causing the diameter to increase relative to normal red blood cells. These sickled red blood cells have a greater propensity to block the microvasculature compromising blood supply to tissues and bones. The resulting vaso-occlusive crisis causes cellular injury via hypoxia, ischemia, infarction, and necrosis. However, recent studies suggest that the pathophysiology of ischemia may be more related to intracellular polymerization rather than cell sickling.[4] It has been postulated that a shortage of oxygen causes membrane damage with resultant potassium efflux and increased cell density.[5] The altered membrane also causes an increased expression of adhesion molecules promoting adhesion of sickle cells to the endothelium. The resulting clumps of cell may reduce blood flow enough that hemoglobin S polymerization, cell sickling, and vaso-occlusion can occur before the blood has passed through the vasculature. Granulocytes interact with the sickle cells and endothelial cells to release injurious cytokines.[6] Activated platelets release thrombospondin, further promoting sickle cell adhesion to the endothelium. Reticulocytes display additional adhesive ligands that facilitate interactions between sickle cells and endothelial cells.[7]

The vaso-occlusive crisis, also known as "painful crisis", is the most common manifestation of SCD. During an episode, the individual experiences severe pain, most commonly involving the extremities, back, and abdomen. The pain usually lasts 5 - 7 days. Sometimes there is an associated low grade fever. Vaso-occlusive crisis may occur spontaneously or may be precipitated by cold weather, anxiety, infection, physical activity, or high altitude. Painful crisis has also been associated with general worries about finances, problems with relationships, lack of social support, and negative life events.[8, 9] There is some variation in the severity of attacks. Approximately 60% of SCD patients report severe pain in a given year while a small number report constant pain.[4]

Many additional manifestations of SCD exist. Acute chest syndrome is a common complication that has been associated with fever, chest pain, cough, rapid or laboured breathing, pulmonary infiltrates, elevated white blood cell count, abdominal bleeding, and vomiting. Other complications include cerebro-vascular accident, convulsions, splenic sequestration, osteonecrosis, leg ulcers, liver and kidney diseases, proliferative retinopathy, priapism, and spontaneous abortion. Hemolytic anemia can occur with associated formation of gallstones and acute aplastic crisis. Infections are also common particularly with *Streptococcus pneumoniae, Salmonella species, Staphylococcus aureus and Escherichia coli.*

### *Children and Adolescents with SCD*

Psychiatric manifestations of chronic mental disorders such as

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SCD normally occur as a result of two major mechanisms: The direct consequences of the illness on brain function and emotional response of the individual to the illness and its consequences in the individual's life. Many children with SCD show signs of vaso-occlusive crisis, splenic sequestration, infection, acute chest syndrome and central nervous system complications. Chronic hemolytic anemia and multi-organ damage has also occurred in children. Furthermore, impaired growth and delayed sexual maturation are common in children with SCD. This may lead to poor self-esteem and subsequent depressive symptoms; specifically, dissatisfaction with one's body image. Children and adolescents with SCD may experience anticipatory anxiety because of the unpredictable course of their condition. As with any other genetic disease, children and adolescents may have known relatives that died from the same illness. The median life expectancy among people with SCD is only 47 years, with the highest mortality rate occurring below the age of 5 years.[10] Children with SCD are at a higher risk for school failure than their healthy peers. This may be due to prolonged absence from school during hospitalization.

Although, the prevalence of clinical depression in children with SCD is unknown, in a study it was found that depression was more common in children with SCD than in the general population.[11] In another study, it was found that more than 25% of children with SCD have depression, anxiety, difficulties with social functioning and poor academic performance.[11] all related to painful episode. The occurrence of subtle pain may be disruptive enough to decrease the motivation necessary for a child to succeed academcially.[12]

Chronic vascular insufficiences or cerebrovascular accidents have also been associated with cognitive impairment among children and adolescent with SCD. In children with SCD, only about 10% demonstrate radiological evidence suggestive of a cerebrovascular accident. It has been suggested that as many as 90% of these children may in fact possess undetectable central nervous system deficits. Children with SCD have been shown to exhibit crossed dominance, visuomotor deficits and decreased attention spans relative to healthy control groups. In addition, spelling and reading skills are significantly worse in children with SCD when compared with matched controls.

As children grow into the adolescent stage, the challenges of living with SCD become more evident. During adolescence, development centres on identity formation. Unfortunately, this is often impeded in individuals with SCD.[12] As a result of repeated episodes of painful crises and subsequent absence from school, it may take a longer period to complete their education. Consequently, they may be forced to depend more on their parents for financial support. Adolescents with SCD tend to be more self-conscious and dissatisfied with their appearance. They tend to fatigue more readily during athletic activities, and may react with pessimistic and hopeless attitudes or become socially withdrawn. This may lead to poor self-esteem and difficulties in forming a satisfying interpersonal relationship.[9]

In a prevalence study, using both the children's depression rating scale (CDRS) and the clinical interview in the same subjects,[14] the prevalence of depressive symptoms were higher among the individuals with SCD when the CDRS was used. However, the depressive symptoms were not found to be higher among the individual with SCD when the clinical interview was used. The reason for these discrepancies are unclear. However, excessive fatigue, physical complaints, poor self esteem which tend to be over represented among people with SCD may not necessarily be screened for in a clinical interview.

In a review of 60 studies involving children and adolescents with chronic medical problems,[15] significant variations in depressive symptoms were found among children with the same disorder. However, children suffering from certain disoders (e.g. asthma, recurrent abdominal pain, sickle cell anemia) may be at greater risk than children with other disorders (e.g. cancer, cystic fibrosis, diabetes mellitus). Disease severity was inconsistently related to depressive symptoms, while time since diagnosis, gender and age were generallly unrelated to symptoms.

In another study[16] consisting of 80 non-hospitalized adolescents with chronic diseases (20 with SCD, 40 with asthma and 20 with diabetes), adolescents with chronic diseases had significantly higher depression scores than their healthy age-matched controls. There was no statistically significant difference in life events between the chronic diseases and control groups. Depression, self esteem and life events did not differ significally among the three disease groups. These findings suggest a need for further studies to address the prevalence of depression and low self-esteem in adolescents with chronic diseases. It is not clear whether the depressive symptoms in individuals with SCD is different from that of other chronic condition. We suspect however, that the severity and frequency of painful crisis may contribute to depressive symptomatology.

***Family members***

The disease process dramatically affects family members as well. The sick children may be perceived as having a physical disability. Thus, additional demands may be placed on healthy siblings of individual with SCD. A stressful environment may result when a brother or sister does not understand why their sibling requires special treatment, receives extra privileges, or spend more time with their parents. The perceived reduction in attention paid to healthy children may also lead to psychopathology. In fact, in one study, Belgrave and Lewis found a higher prevalence of depressive symptoms in healthy siblings of SCD individuals than in the patients themselves.[17]

***Adults with sickle cell disease***

As with children with SCD, the literature is inconsistent regarding the association between SCD and psychopathology among the adult population. The psychological sequelae of SCD may include depression, generalized anxiety disorder, anxiety about one's body image, fear of invasive treatments, a preoccupation with death, self-pity, and low self-esteem. Social functioning may be impaired, resulting in withdrawal from peer relationships and consequent social isolation. Family functioning may also be dramatically affected and the relationships between parents, siblings and children tend to deteriorate.[18, 19, 20]

While some authors have suggested an inconsistent relationship between SCD and depression,[21, 22 23] others had found an increased rate of depression in individuals with SCD.[24] In a study by Ohaeri et al, patients wth SCD were more likely to have low self-esteem, feelings of inadequacy and inferiority and negative life events.[3] Increased life stressors may worsen the complications of SCD and increase the risk of developing depression.[25] Unfortunately, patients with SCD are at a higher risk for experiencing life stressors including financial difficulties, social ridicule, frequent hospitalizations and problems with daily living.[18] Depression among adults with SCD may manifest as irritability, guilt, helplessness, insomnia, weight loss or gain, suicidal ideation, sadness, social withdrawal or somatic complaints.[26]

Depressive symptoms have also been associated with the severity of disease in SCD. In a study of 440 adults with SCD,[27] the percentage of patients with SCD exhibiting significant depressive symptomatology was 43% using the Centre for Epidemiologic Studies - Depression Scale (CES-D). This percentage dropped to 18% when more stringent criteria were used. In another controlled study, evaluating the prevalence of psychiatric morbidity among 38 patients with sickle cell anemia, [28] 63% of the subjects with SCD reported positive psychiatric morbidity while only 21% of the

controls did. The main psychiatric symptoms found were mixed anxiety and depressive symptoms. There are no studies comparing the prevalence of depression among individuals with acute or chronic pain and SCD. However, patients with sickle cell disease who experience frequent painful crisis tend to exhibit problems with self concept, low self esteem, anxiety, depression and dissatisfaction with body image.[29]

The relationship between depressive symptoms and pain has not been defined. Depression often complicates chronic pain and may lower the threshold for tolerance of pain. Depression may also interfere with the ability to cope with pain. Severe pain may cause withdrawal from interpersonal contact and consequent self-absoption. With prolonged pain, the patient may experience anger and resentment especially if he or she believes that pain relief has been withheld. Barbarin et al.[11] found that severity of pain correlated with depressed mood, hopelessness, anger and shame. Additionally, certain patients who take analgesics such as opiates or benzodiazepines for pain management may in fact develop depression resulting from these medications. Patients with SCD who have numerous painful crises may thus be vulnerable to medication-induced depression.

Post traumatic stress disorder (PTSD) is a condition involving recurrent and intrusive recollection of a traumatic event in the form of images, thoughts, perceptions or nightmares. Such individuals avoid stimuli associated with the trauma, and have symptoms of increased arousal such as irritability, difficulty with concentration and hypervigilance. PTSD secondary to sickle cell painful crisis has been described.[30] It has been speculated that the presence of depression and anxiety may increase the frequency of SCD complications, thus making an individual more prone to developing PTSD.[30]

***Treatment strategies***

All patients with SCD should be carefully evaluated, focusing on biological, psychological and social approach, to determine the presence and severity of psychiatric symptoms. Patients should be educated about the pathophysiology and mode of transmission of SCD. This may be done individually with the patient or with other family members present. Family members should be encouraged to be supportive of the patient.[31] Health care professionals need to encourage individuals with SCD to express their feelings about the disease and their medical treatment.

Psychiatric diagnosis in individuals with SCD should be treated with psychopharmacology, psychotherapy and social interventions. Although, we are not aware of any study looking at which psychotropic agent is most effective among these individuals, once a diagnosis is made, treatment should focus on clinical symptoms.

It has been suggested that some children with SCD described as being neurologically normal may include some children who have experienced silent strokes.[32] Another study looking at neuropsychological functioning of 10 chidren with SCD indicates that these individuals experience significant impairment of cognitive functioning following a cerebrovascular accident.[33] Such neurological deficits may not be evident with conventional brain imaging studies such as CT or MRI and may only be evident using the SPECT.[34]

Patients with co-morbid depressive symptoms should be treated with antidepressants and psychotherapy. We are recommending that psychotherapy continue even after depressive symptoms remit in order to prevent relapse. If an anxiety disorder is identified, treatment should include treatment with a selective serotonin reuptake inhibitor with or without an anxiolytic agent. Psychotic symptoms present during painful crisis should be treated with an anti-psychotic medication. Additional adjunctive treatments include rehydration, whirlpool baths and application of heat. Oral analgesics are recommended for mild painful crises; however, more severe crises require parenteral opiate medications. The narcotic medication should be administered at regular fixed intervals rather than as needed. Once the pain subsides, the parenteral medication should be tapered and replaced with an oral agent. Pain should be assessed frequently with a pain-measurement scale such as the visual analogue scale so as to guide treatment.

The treatment of PTSD associated with SCD should follow the traditional treatment for PTSD. Pharmacological treatment strategies should include the use of antidepressants such as the selective serotonin re-uptake inhibitors (SSRIs) as well as time-limited use of benzodiazepines. Beta-blockers, mood stabilizers and antipsychotics may also be effective. Psychological methods of treating PTSD include group therapy, psychodynamic psychotherapy and behaviour therapy. Other strategies include the use of eye movement desensitization and reprocessing (EMDR) and dialectic and behaviour therapy (DBT).

Supportive measures are an integral part of treatment for patients with SCD. These include encouraging patients to attend their outpatient appointments, taking prescribed medications, eating a proper diet, and getting adequate exercise.[17]

Social support is especially important since social isolation increases the chance of developing depression.[36] Social support enhances mental and physical health, facilitates compliance with medical treatments and may decrease symptoms of depression.[17] Since individuals with SCD have been shown to have fewer social relationship,[37] adequate social support is particularly important.

**Conclusion**

SCD is a relatively uncommon condition. Among practitioners, there is lack of awareness of associated psychopathology when compared with other chronic diseases such as diabetes and cancer. SCD and depression can both cause diminished appetite, poor concentration, disrupted sleep, and reduced energy. Careful evaluation is therefore necessary to assess depressive symptoms among individuals who have SCD. Once a psychiatric diagnosis is identified, it should be treated appropriately and not dismissed as a normal response to having a painful debilitating disease.

Comprehensive management of patients with SCD should include adequate social support, appropriate education about the illness and improved communication among health care providers, patients, and their families.

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