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Sickle Cell Anemia & Associated Neurological Complications: A Literature Review

Rodjmar Joseph
Lynn University

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Rodjmar Joseph
Biology
Lynn University

Abstract

Sickle cell anemia, an inherited disorder, causes red blood cells to contort into a disk or sickled shape becoming hard and sticky and obstructing blood flow. As the most common hemoglobinopathy, over 100,000 Americans in the US are affected by sickle cell disease. Sickle cell anemia is an inheritance of the abnormal sickle cell gene genetically transferred from both parents. Sickle cell anemia can be easily diagnosed in DNA through a blood test or genetic screening. With a 1 in 4 chance of inheriting copies of the sickle cell gene from both parents if both biological parents are carriers, the cause of sickle cell anemia is due to a single amino acid mutation due to a nucleotide polymorphism or variation typically due to a protein substitution. Individuals with sickle cell anemia may experience signs and symptoms while they are only a few months old. Common signs or symptoms related to this disease are severe headaches, unexplained numbness, confusion, or dizziness. The pathophysiology of sickle cell anemia or SCA relies on the genetics of endometrial dysfunction, HbS polymerization, sterile inflammation and vaso-occlusion. For inpatient hospital visits, sickle cell disease diagnosis was recorded in about 1.7% of whites, 3.9% of Hispanics and 87.5% of blacks (Fingar et al., 2019). Sickle cell anemia life expectancy is two decades shorter in adults compared to children and young adults. Several complications may arise with those infected by SCA, such areas include gallstones, kidney disease, splenic sequestration and may even cause blindness. There are a few management strategies from vitamin intake to bone marrow or stem cell transplant to subdue pain and complications of sickle cell anemia. Sickle cell anemia is a costly, long term health condition that commonly affects minorities. The low income community makes up approximately 92.5% of inpatient hospital visits for patients diagnosed with SCA. Because sickle cell anemia is a lifelong disease, complications that affect the nervous system of those with SCA

may progress with age further exacerbating any symptoms associated with this disease. Sickle cell anemia has been known to lead to a decrease in cognitive attainment, strokes, and even neurological issues such as neuropathy that can result in paralysis. These reported neuropathies occurring in patients with sickle cell disease; are specific neuropathies like peripheral neuropathy, mental & mandibular nerve neuropathy and mononeuropathy multiple. Studies on cognitive activity provide evidence that individuals with SCA experience cognitive deficits in the absence of any injury to the central nervous system. IQ levels of patients with SCA were reported to be between 4-7 scaled points lower than that of those without the disease. Complications of sickle cell anemia can be fatal.

Introduction

Sickle cell anemia is an inherited group of disorders that cause red blood cells to distort into a disk or sickled shape (Serjeant, 2013). Normal red blood cells which contain hemoglobin, a substance that transports oxygen through the body, are flexible, disc shaped and flow through blood vessels with ease. With sickle cell anemia these cells become hard and sticky, obstructing blood flow (Fingar et al., 2019). During the process of this disease red blood cells break apart, initiating early cell death, later resulting in healthy red blood cell shortage. Red blood cells are replaced about every 120 days however sickled cells commonly die in about 15 to 20 days. Individuals with sickle cell anemia experience pain due to this shortage of healthy red blood cells once the oxygenated blood flow to vital organs is blocked.

Sickle cell anemia is the most common hemoglobinopathy, with over 100,000 Americans in the US affected by the genetic disease (Sundd, Gladwin & Novelli, 2018). As a monogenetic, autosomal recessive disorder that causes complications such as dactylitis, hemolytic anemia and pain crisis; sickle cell anemia has the potential to increase the risk of bacterial infections, organ

damage and stroke (Meremikwu & Okomo, 2016). Although typically in areas where malaria is common, according to the Global Burden of disease study, it was found during a systemic analysis that 176,000 people each year die from sickle cell disease complications, 3.2 million people have sickle cell anemia and 43 million people live with the sickle cell trait worldwide (Sundd, Gladwin & Novelli, 2018). Sickle cell anemia is a lifelong disease and for most people there is no cure however bone marrow or stem cell transplants have been done with limitations due to the high risk involved. Disease management has been set in place to sustain the livelihood of those individuals affected by sickle cell anemia.

Etiology

Sickle cell anemia is an inheritance of the abnormal sickle cell gene genetically transferred from both parents. The sickle cell trait is an inheritance of the abnormal sickle cell gene genetically transferred from one parent and a normal gene genetically transferred from the other parent (Centers for Disease Control and Prevention, 2004). Determination of whether a patient is a carrier or non-carrier, is gene dependent on the inheritance from their parents. If both biological parents carry the mutated gene the child has a 1 in 4 chance of inheriting copies of the sickle cell gene from both parents. Sickle cell disease is a direct consequence when hemoglobin that typically carries oxygen through the body from the lungs through red blood cells are disabled due to the misshapen red blood cells, once sickled. (Mayoclinic, 2022)

The cause of sickle cell disease is due to a mutation on the beta subunit globin gene where there is a single substitution of an amino acid in the sequence; resulting in a poorly soluble tetramer when deoxygenated (Onimoe & Rotz, 2020). The deoxy form of the polymerized hemoglobin occurs from this. Abnormal hemoglobin S is produced instead of normal

hemoglobin A. This substitution occurs in the gene that notifies the body to produce hemoglobin, the iron rich protein in the red blood cells.

Patients with the sickle cell trait are also carriers of the hemoglobin S gene meaning they too can pass the disease on to their child. The inheritance of SCA is also possible when one parent is a carrier of the disease while the other one has it. Typically, individuals with the trait do not have symptoms as they do not necessarily have the disease themselves however the ability for them to experience minor symptoms is not unusual. If both biological parents carry the mutated gene the child has a 1 in 2 chance of inheriting a copy of the sickle cell gene from one parent, becoming a carrier. There is also 1 in 4 chance that the child will not inherit any mutated gene, in turn will not be able to pass it on to their child.

Genetics of Sickle Cell Anemia

Genetically the cause of sickle cell disease involves both homozygosity (HbSS) and heterozygosity (Example: HbC) for rs334 mutations. The sickling form of hemoglobin S, rs334 is the normal adult hemoglobin from of sickle cell disease. Abnormal hemoglobin S, HbS, arose from the genetic mutation that occurs in the amino acid base substitution on the 6^{th} codon on the Beta globin chain of hemoglobin on chromosome 11, causing strands of polymerized hemoglobin. (Williams & Thein, 2018). The genetic disorder, sickle cell anemia, was suggested to have originated from five individual mutations from Africa, India and the Middle East. In these mutations the beta S gene underwent DNA polymorphism, where there is a change in the nucleotide sequence with amino acids GAG to GTG. This single substitution went from a hydrophilic glutamic acid to hydrophobic valine (Maakaron et al.,). This type of genetic mutation is a called a single nucleotide polymorphism (SNP) or single nucleotide variation (SNV).

Sickle cell disease embraces a group of disorders in which pathology results from the inheritance of the sickle cell gene can also be a double heterozygote. Heterozygosity for sickle cell anemia can lead to diminished levels of beta globin production such as Beta thalassemia or other mutations that are precursors of Beta globin structural variants such as HbC (Williams & Thein, 2018).

The most common genotype at birth is the homozygous allele of the sickle cell (SS) disease. Common genotypes of SCA are SC, SS, Sickle-beta zero thalassemia's and sickle-beta plus thalassemia (Onimoe & Rotz, 2020). Common types of anemia in the United States are caused by mutations in the HbS gene and the HbC gene as well as the different thalassemia associated with the blood. Hematologically and clinically, sickle cell Beta thalassemia and sickle cell disease are severe genotypes (Serjeant, 2013).

There is variation in the the severity and frequency of the complications in both genotypes. Immigrated people found in the US effected by SCA are commonly found with some sort of ancestry from Southeast Asian, they typically have the Hb E gene mutation (Braunstein, 2020). The most severe sickle cell type with 60-70% US cases is homozygous HbSS; this type is a two abnormal hemoglobin "S" gene inheritance from both parents (Centers for Disease Control and Prevention, 2004). HbSC sickle cell type is where one abnormal hemoglobin "S" gene is inherited from one parent and one abnormal hemoglobin "C" gene is inherited from another parent; this form of SCA is typically milder. In rare cases of SCA patients have type HbSD, HbSE or HbSO where they have one abnormal hemoglobin "S" gene inheritance and one abnormal O, E or D gene from their parents. There rare types of SCA vary in severity. Common types of anemia in the United States are caused by mutations in the Hb S gene and the HbC gene as well as the different thalassemia associated with the blood (Braunstein, 2020). Individuals

inherit the HbS beta thalassemia type of SCA by one abnormal hemoglobin “S” gene and one beta thalassemia gene (Centers for Disease Control and Prevention, 2004). The “zero” HbS beta gene is a severe form of HbS beta thalassemia in SCA while “plus” HbS beta is the milder form of HbS beta thalassemia in SCA (Centers for Disease Control and Prevention, 2004).

In the sickle cell trait, HbAS gene, there is one hemoglobin S gene inheritance and one normal hemoglobin A gene. This is the gene where there is typically no sign of disease (Centers for Disease Control and Prevention, 2004). Health issues or symptoms commonly occur with stress to the body, this can be through exercise or from dehydration. Parents only pass the abnormal hemoglobin S gene to their child. The quantitative HbF trait is the gene that impacts the severity of sickle cell anemia (Williams & Thein, 2018). The BCL11A gene which suppresses HbF production in adults but increases levels of fetal hemoglobin use gene therapy to reduce severity in the disease (Williams & Thein, 2018).

Diagnosis

Sickle cell disease can be easily diagnosed in DNA through a blood test. Although the main form of diagnose of SCA, if blood test results are not clear enough, genetic screening can be done. (Centers for Disease Control and Prevention, 2004). These test can also tell whether you carry the full gene or the trait and how many copies of the sickle cell gene an individual has.

With access to more advanced technology, diagnosis of sickle cell disease for women pregnant in the United States can be done as early as in utero while a mother is pregnant The sickle cell trait is an inheritance of the abnormal sickle cell gene genetically transferred from one parent and a normal gene genetically transferred from the other parent (Centers for Disease Control and Prevention, 2004). During in utero diagnosis of sickle disease from no earlier than 8 to 10 weeks, testing can be done one of two ways; one way is amniocentesis where a sample of

the amniotic fluid that the fetus is encapsulated in is tested. Another way in utero diagnosis is completed is through a sample of the placenta; this is called Chronic villus sampling where both genetic and chromosomal abnormalities can be tested (Singh et al., 2015). Early diagnosis of SCA is emphasized as children are at higher risk of infection.

Sickle cell diagnostic testing vary depending on the patients age. Diagnosis of SCA can be done in newborns through neonatal screenings and in young adults or older, the diagnosis can occur through peripheral blood smear, hepatobiliary function test and hemoglobin solubility test. Compared to in utero screening, newborn diagnosis can predict the severity of the sickle cell anemia (Maakaron et al.,2021).

Diagnosis can be done through high performance liquid chromatography, capillary electrophoresis, isoelectric focusing and gel-based electrophoresis (Williams & Thein, 2018). Most of those methods of diagnosis are used when performing blood test. Sickle cell disease can also be diagnosed through imaging studies such as MRIs, CT scans and radiography. When issues with diagnosis arose for reasons such as lowered sensitivity, different approaches involving next-generation sequencing analysis and tandem mass spectrometry were developed (Williams & Thein, 2018). Additionally, sickle cell anemia can be diagnosed through transcranial near-infrared spectroscopy or cerebral oximetry, echocardiography and transcranial Doppler ultrasonography as well. (Maakaron et al.,2021).

Abdominal ultrasonography for SCA diagnosis is typically used to eliminate an ectopic pregnancy or complications such as cholelithiasis and cholecystitis (Maakaron et al.,2021). Pulmonary hypertension can be recognized through echocardiography in individuals with sickle cell anemia. Through transcranial near-infrared spectroscopy or cerebral oximetry, effected children have the opportunity to be screened for cerebral venous oxygen saturation. Transcranial

Doppler ultrasonography is a screening used for children with SCA that have a greater risk of stroke. Although MRIs are typically used for bone marrow detection they can be utilized to monitor changes of acute or chronic infarctions as well as osteonecrosis, marrow hyperplasia and osteomyelitis. Radiography, as a form of diagnosis is valued for its detection of respiratory symptoms. (Maakaron et al., 2021)

Lab testing performed on patients with sickle cell anemia are including but not limited to hemoglobin electrophoresis, peripheral blood smear, serum electrolytes, hemoglobin solubility testing and blood cultures. Kidney function of individuals affected by this disease can be evaluated through urinalysis, BUN and creatinine testing (Maakaron et al., 2021). Diagnosis of sickle cell anemia is commonly associated with further health complications making it necessary to expand testing into other fundamental mechanisms of the human body. Early detection of sickle cell anemia is beneficial for patients to start managing complications, considering it is incurable.

Signs & Symptoms

Individuals with sickle cell anemia may experience signs and symptoms as early as 6 months of age. Early signs or symptoms that relate to this disease are severe headaches, unexplained numbness, confusion, or dizziness. Patients may also experience issues walking or slurred speech, malaise and fatigue. Paralysis or weakness on one side of the face, arms or legs are also key indicators or blood pressure issues associated with sickle cell anemia (Mayoclinic, 2022). SCA symptoms can be exacerbated by a few external and internal reasons such viral infections, localized trauma or fever (Braunstein, 2020). Due to lack of blood circulation patients may experience dactylitis, which is swelling in the feet and hands (Meremikwu & Okomo, 2016). With a shortage in the healthy red blood cells a delay in puberty or a stunt in growth in

children and babies may be occur. The blood vessels in the eyes may also be affected by the sickled cells, causing damage to the retina leading to issues with vision.

When oxygenated blood flow to the vital organs is blocked due to sickle cell disease causing pain, the individual experiences a “pain” crisis; crisis can also be triggered by circumstances associated with low blood volume or increased blood acidity (Fingar et al., 2019). Typical pain crisis triggers involve stress, alcohol, smoking, pregnancy, infections, strenuous exercise, dehydration, sudden temperature change or other medical conditions. These crises episodes vary in severity and length of time in each person, it may even progress or diminish over time (Fingar et al., 2019). The pain individuals experience is aggressive enough to put them in the hospital once the pain becomes too severe. This significant and common symptom of SCA may become chronic in some people causing damage to the joint and bones as well as formulating ulcers.

When symptoms affect the mobility or vision of an individual it is advised to seek medical attention as soon as possible. An individual should seek a doctor when they experience a stiff neck, a painful erection for hours, slurred speech, yellowing in the eyes or skin, difficulty breathing or weakness in the body. It is important to pay special attention to children as they are prone to infections, typically initiate by fevers that can turn fatal (Mayoclinic, 2022).

Pathophysiology

The pathophysiology of SCA relies on the genetics of endometrial dysfunction, HbS polymerization, sterile inflammation and vaso-occlusion. The initial approach is to better understand the biomolecular and biophysical mechanisms of hemoglobin polymerization. The studies on molecular and cellular mechanisms of sickle cell disease have motivated the evolution of vaccinations and prophylactic therapies (Sundd, Gladwin & Novelli, 2018). Other

physiological processes associated with SCA is hemolysis, endometrial dysfunction and blood vessel occlusion (Williams & Thein, 2018). All of these which can potentially lead to multiorgan issues.

Vaso-occlusion or cell adhesion is a blood vessel occlusion that can lead to ischemia in patients with sickle cell disease is the number one cause of "pain" crisis in patients (Sundd, Gladwin & Novelli, 2018). As a key mechanism that encourage the clinical aspect of sickle cell anemia, HbS polymerization modifies features of the red blood cells that initiate the obstruction of blood flow, potentially harming our vital organs. Endometrial dysfunction occurs when oxidative stress is present in the blood vessels and cell of individuals with SCA.

Sterile inflammation in individuals with SCA is initiated by the release of cytokines (inflammatory molecules) and the activation of red blood cells. Due to main role inflammations plays in the pathophysiology of SCA, evidence suggest anti-inflammatory drugs may soon replace therapies, transplants and transfusions (Conran & Belcher, 2018). Numerous inflammatory responses are results of complications experienced in SCA; these are including but are not limited to auto splenectomy, pulmonary hypertension, nephropathy, leg ulcers and acute chest pain (Conran & Belcher, 2018). The pathophysiology of SCA is contingent upon ones' genetics.

Sickle Cell Anemia and the Nervous System

Although neuropathies are not common in patients with sickle cell disease, there have been reports of them occurring in patients with sickle cell disease; specific neuropathies such as peripheral neuropathy, mental & mandibular nerve neuropathy and mononeuropathy multiplex are the few commonly associated with the disease (Ballas & Darbari, 2013). It is expected for individuals with SCA to experience neuropathic pain in the central nervous system due to their

relations however that is not the case. The few complications associated with SCA and the CNS are cerebral intracranial hemorrhage, hearing loss, cognitive dysfunction, spinal cord infarction and cerebral infarction (Ballas & Darbari, 2013).

To avoid further complications, it is advised of individuals with SCA to seek neurological care early. A preliminary approach for treatment of neurological complications that may arise in individuals due to SCA is the use of aspirin. Although continued use of aspirin could put a patient at risk for intracranial hemorrhage, it reduces ischemic activity that is recurrent (Alroughani et al., 2016). Patients should seek professional medical help for advanced treatments such as hydroxyurea and red blood cell transfusions. Further neurological complications in SCA are including but not limited to moyamoya, brain infections, SCA delirium, SCA psychosis and brain atrophy (Alroughani et al., 2016).

As a frequent symptom in patients with sickle cell anemia, the direct cause of headaches has yet to be determined. The question still remains whether is it related to stress, the anemia or circulation. Because of the decrease in blood flow and the constant low state of hemoglobin in the blood headaches remain common.

Neuropathic and nociceptive pathways have said to be involved in neuropathic pain. According to Al Jafar in his study nociceptive pain is a result of noxious stimuli activation of nociceptor sensory receptors. Neuropathic pain is due to damage to the central and peripheral nervous system or a malfunction in the nervous systems communication (Ballas & Darbari, 2013). The symptoms associated with neuropathic pain is tingling or numbness, the sensation of pins and needles or hyperalgesia.

Hemorrhagic strokes due to neurologic injury or a brain bleed is also a possible neurologic symptom of sickle cell anemia. Potentially leading to aneurysms, subarachnoid

hemorrhage or intra cerebral hemorrhage are associated with the impairment of the coagulation profile in sickle cell anemia. Ischemic stroke has been reported in about 8 to 11% of SCA cases involving children (Alroughani et al., 2016). These symptoms due to a minor neurological dysfunction in the brain include aphasia, cranial nerve palsy, seizures and even a coma. Strokes are an isolated event and can occur without any warning. Twenty-year-old patients who are carriers of the hemoglobin HbSS gene type are 11% more likely to have an overt stroke; 24% of patients with the same gene type would have had an overt stroke by the age of forty-five (Brandow & Liem, 2022). TIAs or transient ischemic attacks is a neurologic deficit that can last anywhere from 1 to 24 hours. This infarctive occurrence is typically difficult to be discovered radiographically so it is commonly diagnoses through symptoms such as seizures and migraine. TIAs in may appear to resemble muscle spasms in radiographic studies (Alroughani et al., 2016).

Moyamoya or spontaneous occlusion in the arteries according to Al- Jafar and his group, is a rare neurological condition characterized by cerebral vasculopathy. Commonly found in patients with sickle cell disease but not limited to those with the trait, moyamoya is a blockage in the arteries at the base of the brain due to restricted blood flow. Symptoms include typical neurological signs of complications such as headaches, seizures, paralysis, weakness, cognitive delays and visual disturbances (Alroughani et al., 2016).

Brain atrophy, characterized by neuron loss due to shrinking of the brain is a serious complication experienced by patients with sickle cell disease. Damaged or lost brain cells cannot be recovered, resulting in permanent trauma of SCA. Symptoms include difficulty speaking, loss of motor skills, seizures, dementia and comprehension delays (Alroughani et al., 2016).

Delirium, or state of confusion, in sickle cell disease is characterized by conscious disturbance or cognitive changes that progress over a period of time. Frequently affecting older

individuals with SCA, delirium is common in 1 to 10 patients already hospitalized by SCA. Psychosis, associated with losing touch with reality is a neurological complication found in SCA patients as well. Because of the sickling and physiological processes affiliated with this disease, psychosis causes complications or isolation in the brain tissue. Psychosis is diagnoses by hallucinations or the act of feeling, hearing or seeing things that are not present (Alroughani et al., 2016).

Morbidity in sickle cell disease individuals is significantly affected by silent cerebral infarcts and overt strokes. The diagnosis of both an overt stroke and silent cerebral infarct is tested by an MRI; it is confirmed by the presence of acute infarct. Large arteries, intracranial internal carotid arteries and middle cerebral arteries are involved in overt strokes; while the penetrating arteries are involved in silent cerebral infarction (Brandow & Liem, 2022). Infarction in patients with SCA are often experienced in the deep white matter or cortex of the brain compared to infarctions occurring in patients without SCA who experience them in the brains stem, thalamus and rarely the cortex. By 18 years old 39% of individuals with SCA will have cerebral infarcts and 50% by 30 years old will have cerebral infarcts (Brandow & Liem, 2022). Women and adults are more at risk of silent cerebral infarction compared to young adults. Major neurocognitive impairments are necessary in individuals after experiencing an infarctive stroke. Each silent cerebral infarction an individual experience as a result of SCA, they jeopardize their neurocognitive outcomes. It is possible for patients with SCA to be at risk of cognitive impairment in the absence of silent cerebral infarction which has the potential to become worse as they age, affect their life quality

There has been evidence found of neurobehavioral and cognitive deficits in patients with SCA even though they have not experienced any cerebral accidents; causing researchers to

believe there are cellular mechanisms going undetected. According to resent studies, patients experiencing different chronic hematological diseases are 20% less likely to express poor educational attainment, depression or anxiety than in those individuals who have SCA (Hardy et al., 2018). It was also suggested that neurobehavioral complications and cognitive impairments observed in patients with sickle cell disease could be due to both the chronicity and pain of the disease (Hardy et al., 2018). Studies on cognitive activity provide evidence that individuals with SCA experience cognitive deficits in the absence of any injury to the CNS. Through the results, it has been suggested that slower processing time is in direct relation to white matter integrity loss. IQ levels of patients with SCA were reported to be between 4-7 scaled points lower than that of those without the disease (Stotesbury et al., 2018). Adults and children with sickle cell anemia have been found to have lower cognitive scores on test and are susceptible to have lower academic attainment. Findings such as these suggest that sickle cell anemia may directly relate to cognitive impairment in patients that experience vessel occlusion, strokes and metabolic inflammation. Current evidence suggests that 45-year-old adults and older with SCT (also the same has having SCA) are at risk of developing cognitive impairments as they age, reducing normal cognitive function (Cahill et al., 2019). Cognitive functions are assessed by memory, executive and learning function scores that test longitudinal changes and global cognitive activity in the brain (Cahill et al., 2019). Damage to the CNS through strokes, cognitive impairment and silent cerebral infracts are typically the most permanent trauma of SCA. Between 10 to 20% of adults 40 years or older with the homozygous or heterozygous hemoglobin SS gene have experienced a cerebrovascular incident at some point (DeBaun et al., 2020).

Although there are few, the complications associated with sickle cell anemia and the central nervous system such as the specific neuropathies, cognitive dysfunction, cerebral

intracranial hemorrhage, hearing loss, spinal cord infarction and cerebral infarction can be fatal. SCA can affect the CNS and blood flow due to limited circulation in the blood vessels reducing oxygen in the brain and other parts of the body. The use of certain over the counter medication has been advised for continued use to reduce recurrent ischemic activity, all risk considered. Neurological care in early sickle cell anemia diagnosis has also been advised to seek in efforts to avoid further complications, Theses further neurological complications in SCA are including but not limited to brain atrophy, brain infections, moyamoya, SCA delirium and SCA psychosis. With little evidence to support the claim that SCA causes severe headaches this symptom continues to taunt patients, it has considered to be a complication due to the hemorrhaging and low blood flow circulation. Neuropathic pain is not extremely common in SCA however when apparent neuropathic and nociceptive pathways ae involved. A hemorrhagic stroke is a more common neurologic symptom of sickle cell anemia. Artery blockage in moyamoya may after individual with both sickle cell anemia and the trait. Brain atrophy, a more dangerous neurological complication of SCA may result in permanent damage. Cognitive changes and conscious disturbance in sickle cell disease progress with age and time. Cognitive attainment for carriers of SCA experience a decrease in memory and processing further lowering their IQ compared to others who are not carriers. These finding had a direct correlation to patients with SCA with increased insecurities, anxiety and depression. Sickle cell anemia does not have a direct cure and damage to the central nervous system is permanent. Research efforts are taking place in treatment and preventions options for SCA, more efforts could be placed in complications that arise in the CNS due to SCA. For example, care management in cases that result in neuropathy or methods on improving already damaged cognitive abilities or methods to stabilize cognitive processing to avoid further damage.

Sickle Call and Race

Sickle cell anemia affects 1 in every 350 black children (Onimoe & Rotz, 2020). Each year over 220,000 babies are born with sickle cell disease in Africa, affecting 1 in 2000 live births, killing most by the tender age of 5 (Meremikwu & Okomo, 2016). In the Hispanic culture SCA affects 1 in every 16,300 American births. African Americans were reported to have the highest amount of inpatient hospital stays with check ins reported at 87.5% compared to Caucasians with 1.7% and Hispanics with 3.9% of check ins for patients with SCA. It was recorded in 2016 that approximately 90 percent of sickle cell disease related stays were of black individuals (Fingar et al., 2019).

1 in every 3 adults are carriers of this disease in sub-Saharan African, often affecting those of the Mediterranean, sub-Saharan, Caribbean, Asian and Indian decent (Meremikwu & Okomo, 2016). William and Thein found recently that SCA is a significant contributor to health issues in multiple regions beyond its original geographic origins through global population migration. This include Brazil, the United Kingdom, the United States, France the Caribbean Islands and parts of European countries. Sickle cell anemia is also found in some parts of Southern Turkey, Greece and Sicily, coincidentally these areas are prevalent with malaria.

With higher frequencies in equatorial Africa and low frequencies in the north and south, the sickle cell trait is extensive throughout the continent. The sickle trait alone affects almost 10 to 30 percent of Africa's population and is commonly found in areas where malaria is prevalent (Meremikwu & Okomo, 2016). Reaching its highest presence in the eastern Province, the sickle cell trait is widespread in Saudi Arabia. According to Serjeant, the trait often occurs in central India amongst the tribal peoples with a minor group south of the country. This central group

consist of Western Odisha, Maharastra, Chhattisgarh, Madhya Pradesh and southeastern Gujarat while the southern group involves Kerala and northern Tamil Nada.

Sickle cell disease is predominantly homozygous, SS in India and Arabian Gulf. High frequencies of rs334 were found in parts of India, the Mediterranean basin, the Middle East and sub-Saharan Africa with 10 to 20% rates.

Sickle Cell and Age

The life expectancy of individuals with sickle cell anemia is about two decades shorter in adults compared to children and young adults. The median age of death for individuals with SCA is 42 years old for women and about 48 years old for men; keeping the life expectancy on average between 42-47 years old (Meremikwu & Okomo, 2016). In severe cases, the average life span for an individual with SCA related issues is 30 years old. In Africa 50% of children die before they make it to their first birthday (Meremikwu & Okomo, 2016). In England about 350 babies are born each year with sickle cell anemia.

Symptoms of sickle cell disease tend to worsen between the ages of 18-34; there was a recorded 37.2% diagnosis for inpatient hospital visits in the early 2000s. An average of 30% patients aged 40 years old but younger than 65 years old, experience compromising cardiac function. (Fingar et al., 2019).

The most inpatient stays belonged to the young adult age group with a 41% increase from 2000-2014 with an increase in stays for adults 64 and older (Fingar et al., 2019). Between 2000 – 2016 inpatient stays involving sickle cell disease for patients 45 years or older more than doubled in SCA diagnosis admission rate (Table 1). (Michas, 2019).

Number of Patient Admission Rate by Age Per Year					
	2000	2004	2008	2012	2016
1 Years Old +	26,900	28,800	24,800	27,500	25,700
18 Years Old +	46,300	50,100	50,000	63,100	67,900
35 Years Old +	19,200	17,400	15,700	18,000	19,700
45 Years Old +	8,000	11,400	13,100	14,900	17,700
65 Years Old +	1,000	1,400	1,300	2,100	2,900

Table 1: This table depicts the number amount of stays recorded for patients by age diagnosed with sickle cell disease between the year 2000 to 2016. (Michas, 2019).

Strokes or other fatal symptoms of sickle cell anemia may be experienced as early as 6 years old with more problems beginning to emerge by early adolescence. Common symptoms can prevail as early as 5 months old and may begin to plateau around the age of 65 and older (Figure 1) (Michas, 2019). For adults from the age of 18 to 44, a record high hospital readmission rate was recognized compared to other age groups (Fingar et al., 2019).

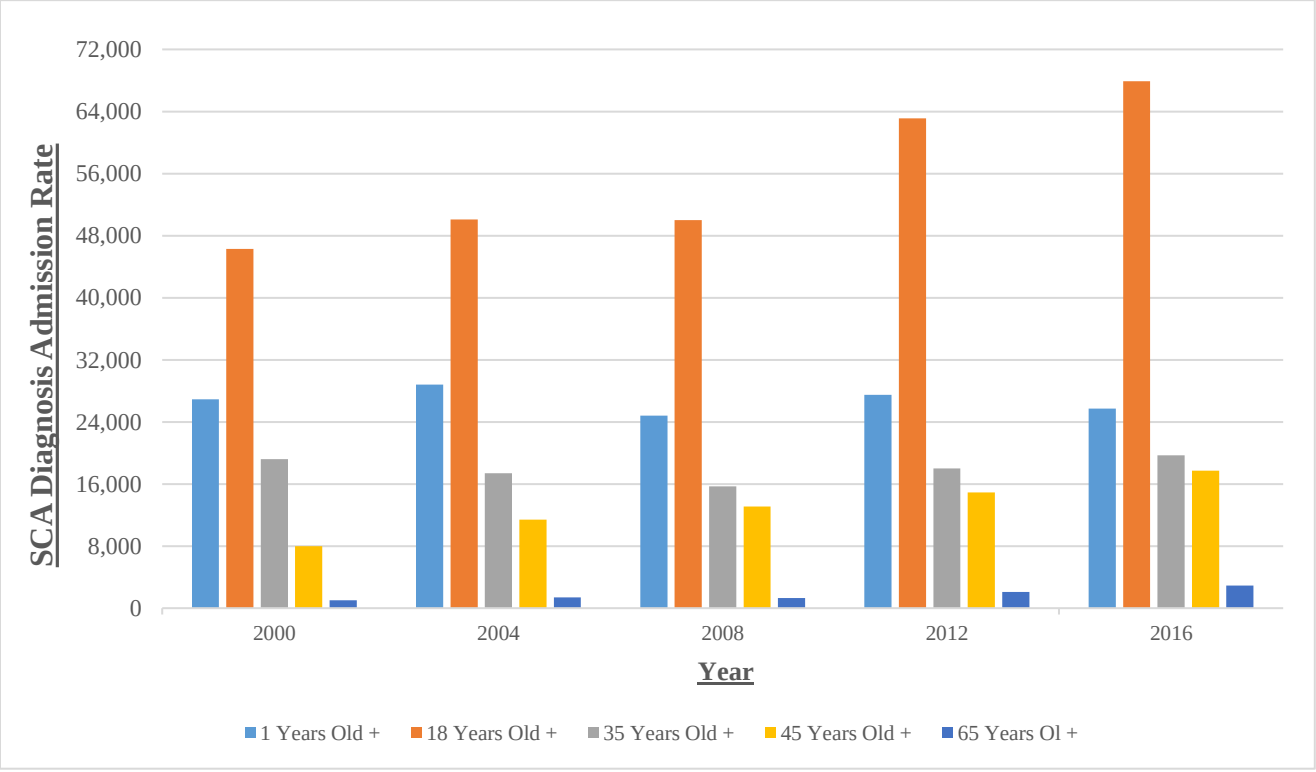

Figure 1: Admission rate of patients diagnosed with sickle cell disease. This figure depicts the recorded amount of hospital admission rates for patients of all ages diagnosed with sickle cell disease between the year 2000 to 2016. (Michas, 2019).

Complications

Several complications may arise with those infected by SCA, affecting areas or organs of the body that people did not think would be affected, see table 2. These are included but are not limited to gallstones, kidney disease, splenic sequestration and blindness. A few other complications of sickle cell anemia are chronic anemia, leg ulcers, retinopathy, pain in the bones and avascular necrosis to name a few (Onimoe & Rotz, 2020).

Sickle cell anemia may also cause pregnancy complications increasing blood clots or high blood pressure in soon to be mothers; or priapism in men. Priapism causes erections in men with sickle cell disease that are long lasting resulting in pain due to the blockage of blood vessels in the penis (Mayoclinic, 2022).

Due to its relation to blood pressure, sickle cell disease may also cause pulmonary hypertension or deep vein thrombosis in patients (Mayoclinic, 2022). Vaso-occlusion, a blood vessel occlusion that can lead to ischemia in patients with sickle cell disease is the number one cause of pain crisis in patients (Sundd, Gladwin & Novelli, 2018). SCA complications in the central nervous system may be managed in the same way strokes can. Individuals may seek lifelong chronic transfusions.

Treatment, Care Management and Prevention

There are a few management strategies from vitamin intake to bone marrow or stem cell transplant to subdue pain and complications of sickle cell anemia (Onimoe & Rotz, 2020). Treatment is necessary to reduce mortality and morbidity in patients with sickle cell disease. A few pharmaceutical inventions such as pneumococcal vaccines, penicillin prophylaxis,

hydroxyurea and malaria chemoprophylaxis have been developed to help prevent sickle cell crisis (Meremikwu & Okomo, 2016).

Home care treatment is a for of care management for less aggressing cases of SCA. Over the counter medications such as aspirin, ibuprofen, alive or Tylenol can be taken to manage pain and minor symptoms. Other ways to manage mild symptoms at home include rest, heating pads, warm baths, staying hydrated and massages.

In cases of extreme pain or symptoms where at home care management is not working seeking a doctor is advised. During this hospital visit a provider may check for infection, fever, crisis triggers or dehydration. For pain patients may be prescribed more aggressive pain medication such as oxycodone, codeine or other nonsteroidal anti-inflammatory drugs depending on their level of pain. In severe cases, providers may prescribe meperidine, hydromorphone or morphine; where patients are in a fatal state of a crisis blood transfusions may be required.

Although a crisis or sickle cell anemia itself is not preventable, there are certain ways to reduce the risk of having a crisis. It is always highly recommended to take all vitamins and medication prescribed by the doctor, avoid smoking, avoid drinking, avoid infection by staying clean, manage stress, stay hydrated and stay warm in low temperature weather.

Four possible pharmaceutical inventions for crisis prevention have been administered in the United States. Pneumococcal vaccines are used in infants starting from the age of 2 months old and recommended to be used routinely. There are two types of pneumococcal vaccines, pneumococcal conjugate vaccines and polyvalent polysaccharide pneumococcal vaccines (Meremikwu & Okomo, 2016). Polyvalent polysaccharide pneumococcal vaccines are specifically recommended to be used in children 2 year and older. Penicillin prophylaxis is a method used in children with SCA that is five years or older to reduce infection as they are more

susceptible and this will aid in decreasing the bacterium Meremikwu & Okomo, 2016). Hydroxyurea has been shown to reduce a few complications brought on by SCA however it has yet to be confirmed if there are long term effects of the drug. Malaria chemoprophylaxis, the regimen involving the consumptions of a medication before, during and after traveling to an area with high malaria rates. Although considered to be useful, malaria chemoprophylaxis is still being evaluated on its effects and benefits of consumption (Meremikwu & Okomo, 2016).

Strategies on therapeutic treatment has been sought out to target sickle cell disease. The initial approach is to better understand the biomolecular and biophysical mechanisms of hemoglobin polymerization. The studies on molecular and cellular mechanisms of sickle cell disease have motivated the evolution of vaccinations and prophylactic therapies (Sundd, Gladwin & Novelli, 2018).

Medical Care

As a neglected disease, sickle cell anemia is a costly, long term health condition that commonly affects Hispanic and African American people (Lee et al., 2019). The low-income community makes up approximately 92.5% of inpatient hospital visits for patients diagnosed with sickle cell anemia and its complications. About 31.4% of these patients went to hospitals in rural areas, 52.4% of the patients went to hospitals in metropolitan areas and the remote hospitals took in about 16.2% of these patients (Fingar et al., 2019). It was discovered that the majority of sickle cell anemia related stays for individuals in the metro community actually transpired in metro area hospitals; whereas 50% of sickle cell anemia related stays for individuals from rural communities transpired in metro area hospitals as well.

Limited access to proper medical care is a common challenge people with sickle cell anemia encounter (Lee et al., 2019). Comprehensive care for those infected by this disease is

scarce due to the lack of expertise in health care providers today. Rural communities with low-income areas experience the backlash of improper care as their resources are limited. People in these areas typically depend on Medicaid and Medicare to cover their medical care, with specialized health care limited on coverage with these plans; there is not sufficient care being provided (Lee et al., 2019). With these limitations individuals with sickle cell disease result to visiting hospitals and emergency departments. Because SCA is both a socially and medically complex illness that continues to affect carriers of the gene mutation throughout their lives, it is imperative adult care is prioritized (Kanter et al.,2020). Because of the limitations for health care in most of the United states, there is an increase of early mortality in patients, care utilization and disjointed care delivery. There is need for more specialized health care providers in hematology to apply adult care to individuals with SCA (Kanter et al.,2020).

In 2014 alone there was a recorded 250,000 hospital visits of patients with sickle cell anemia; with a readmission rate of 80% between a 14 – 30-day turn around compared to a 12.5% non-disease related readmission rate (Fingar et al., 2019). Most of those readmitted were originally admitted through the emergency department compared to normal admission. According to a statistical research on inpatient hospital stays involving sickle cell disease, 134,000 disease related stays were recorded in 2016 with three-fourths plus of these stays involving pain crisis (Fingar et al., 2019). Inpatient hospital stays averaged about 5 days in length for adults and 4 days for children, with a discharge rate that was four times higher than non-disease related stays (Fingar et al., 2019). Most of the hospital emergency room intakes recorded were of patients with sickle cell disease compared to those without the disease.

Conclusion

Worldwide, 176,000 people each year die from sickle cell disease complications, 3.2 million people have sickle cell anemia and 43 million people live with the sickle cell trait. The cause of sickle cell anemia is due to a single substitution from glutamic acid to valine. As a lifelong disease, sickle cell anemia has no cure however bone marrow or stem cell transplants have been considered with limitations because of the high risk involved. If both biological parents carry the mutated gene, a child has a 1 in 4 chance of inheriting copies of the sickle cell gene from both parents. Because sickle cell anemia is commonly associated with further health complications further investigation into fundamental mechanisms of the human body have been initiated. To start managing complications, it is advised that individual get annual check-ups for early detection of sickle cell anemia. Due to lack of blood circulation patients may experience dactylitis or headaches. SCA symptoms can be exacerbated by a few external and internal reasons such viral infections, localized trauma or fever. Further physiological processes associated with SCA is blood vessel occlusion, endometrial dysfunction and hemolysis. The median age of death for individuals with SCA is 42 years old for women and about 48 years old for men; keeping the life expectancy. To reduce mortality and morbidity in patients with sickle cell disease treatment is recommended. With limited access to proper medical care, people with sickle cell anemia struggle. To avoid further complications, it is advised patients seek neurological care. Adults and children with sickle cell anemia have been found to have lower cognitive scores on test and are susceptible to have lower academic attainment. These findings suggest that sickle cell anemia is directly related to cognitive impairment in patients.

	Sickle Cell Anemia Complications
Bone Tissue	SCA may cause avascular necrosis due to
Hand-Feet	Swelling due to blood flow blockage in the blood vessels, commonly found in toddlers and infants
Kidneys	Due to reduced blood flow and lack of oxygen loss of function occurs, affecting filtration of waste
Legs	In combination of infection and inflammation ulcers may become present due to poor circulation in the blood vessels
Liver	SCA increase complications such as gallstones, cholangiopathy and viral hepatitis
Lungs	Life threatening complications may occur due to blood vessel blockage or infection, causing breathing issues
Spleen	SCA may cause enlargement due to an excessive amount of trapped sickled cells
Eyes	Vaso-occlusion of the small vessels may cause blindness
Bones	When blood does not reach the bone causing joints to narrow and to possibly collapse
Heart	SCA can increase the risk of pulmonary hypertension affecting the lungs as well. It causes tricuspid valve regurgitation and ventricle dilation
Brain	SCA can increase the risk of silent cerebral infarctions or seizures. Causing cognitive dysfunction and memory attainment.
Penis	SCA may cause extended, painful erections in men due to blood flow blockage in the blood vessels
Pregnancy	Women may experience blood clots and high blood pressure , increasing the risk of a miscarriage or still birth

Table 2: This table provides minor details on where in the body sickle cell anemia may cause complications and how. (Centers for Disease Control and Prevention, 2004) (Mayoclinic, 2022) (Maakaron et al., 2021)

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