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RESEARCH ARTICLE

FORCE FIELD MODEL ANALYSIS OF SICKLE CELL ANEMIA DISEASE

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ABSTRACT

Sickle Cell Anemia Disease is an autosomal recessive heredity disorder and it is a growing global health concern. It mainly affects people of African & African American descent, but it does affect people from the Mediterranean, the Middle East, the Caribbean, and Central and South America. Sickle cell anemia transforms healthy red blood cells into deformed sickle cells that restrict or completely obstruct the blood vessel causing weakness, susceptibility to infection, stroke, acute chest syndrome, and death. The highest mortality rates are in young children and infants. There are pain-suppression treatments for sickle cell anemia with the most prominent treatment being a bone marrow transplant from a matched donor, but there is yet to be a permanent cure. Mitigating drugs for sickle cell anemia include hydroxyurea and penicillin prophylaxis, but the drugs are not in commercial use and can sometimes not work due to mutagenicity of the disease. There are various levels of prevention such as genetic counseling and education, and newborn diagnostic screening. Due to various factors such as age, heredity, vitamin D levels, and even air pollution the clinical care knowledge and resources to handle sickle cell admissions is severely deficient. This makes sickle cell anemia remains one of the most misunderstood, silent killers on the planet.

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INTRODUCTION

Sickle cell anemia is the hemolytic anemia that has the characterization of abnormally shaped or 'sickled' red blood cells that are removed from circulation, destroyed at increasing rates, and leads to anemia (weakness/fatigue from decreasing blood cell count). Sickle cell anemia can cause vasoocclusion leading to tissue ischemia (restriction or semi-curbing of blood to the tissues) and infarction (obstruction or near full blockage of blood to the tissues). Sickle cell anemia is inherited from a person's parents and is an autosomal recessive disorder.

The dominant abnormality of sickle cell anemia is that the sickled red blood cells have the presence of abnormal sickle cell hemoglobin which is known as HbS. When HbS happens to be deoxygenated, the HbS becomes insoluble to the point that it forms aggregates with other hemoglobin molecules inside the red blood cells. The aggregates of the abnormal sickle cell hemoglobin (HbS) can transform themselves into long HbS chains and that is where the distorted sickled shape takes form and hurts the body through impairing blood vessel flow. Deformed red blood cells will adhere to the endothelium and increase the vasoocclusion, ischemia, and the risk of tissue infarction.

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According to clinical research studies, the complications and difficulties of the vasoocclusion is more painful and harder to overcome than the anemia (Lonergan, 2001). Some common symptoms of sickle cell anemia include severe hemolytic anemia (fatigue and pallor), pain crisis (episodes), susceptibility to serious infections, stroke, and chronic damage to the lungs, bones, and kidneys (Olney, 1999). It is not fully known in detail how many infants, adolescents, and adults specifically die from sickle cell anemia because patients can die from other complications such as vasooclusion, stroke, and other infections (e.g. pneumococcal kinds) and bodily damage from being so weak and vulnerable from sickle cell anemia. However, only 33% of children with sickle cell disease receive appropriate monitoring for stroke risk, 25 percent of child patients did not receive the pneumococcal vaccination (recommended for children under 5 years), more than 75% of adult patients with recurrent pain episodes failed to get hydroxyurea (recommended treatment), and a study in the United States found that even with universal screening for sickle cell disease in 30.8% of cases, long term follow-up after diagnosis was not performed.

Pathophysiology of Sickle Cell Anemia: A first-time historical account of sickle cell anemia was discovered and recorded in 1910 by James G. Herrick. Herrick had described clinical and hematologic manifestations of the disease in a 20 year old dental student from Grenada, but in 1949 Linus

Pauling published a research paper titled, "Sickle Cell Anemia, a Molecular Disease", detailing the point mutation in the beta chain of the hemoglobin molecule. This point mutation caused one single amino acid substitution of valine for glutamic acid in the Beta globin chain and when this substitution is present on both chromosomes of the patient, the result in sickle cell hemoglobin of HbS. If a patient possesses two of the sickle cell hemoglobin genes (HbSS), this is where sickle cell anemia occurs and finally a patient can be heterozygous possessing one normal hemoglobin (HbA) and one sickle cell Beta globin chain (HbS) that will be designated as HbSA (Lonergan, 2001). This is why sickle cell anemia is the first recorded and known disease to have a molecular basis due to its point mutation changing its molecular structure.

Clinical Variability & Presentation of Sickle Cell Anemia: There are many complex arrays of abnormal hemoglobin chain interactions, red blood cell membrane permeability changes, endothelial adhesion, vascular occlusion, and increased hemolysis from the one point mutation of sickle cell anemia causing a single amino acid substitution (Lonergan, 2001). This makes sickle cell anemia very difficult to find any cures or treatments to stop it. Sickle cell disease branches out to any patient that possesses one single HbS chain and one other abnormal beta globin chain, which can also be a sickle cell beta chain. In this case, this patient by Mendelian genetic definition would be HbSS which is sickle cell anemia, have the genotype HbSC, or one of the thalassemias (Hb-S-thai). What makes sickle cell anemia and disease even more complex is that there are other much less common abnormal Beta globin chains and they can combine with a sickle cell Beta chain producing rarer forms of sickle cell disease like HbSD. It has been statistically proven that the HbSS genotype accounts for 60% to 70% of the cases of sickle cell disease in the United States and is the most severe as far as clinical manifestations of any variants of sickle cell anemia and disease. There is a benign condition for sickle cell particularly the combination of the heterozygous HbSA plus one abnormal sickle gene designated S plus one normal hemoglobin gene designated A. With this combinations there is no promotion of vasoocclusion or restriction of blood to the tissues that can cause organ damage.

Sickle cell's HbS has been known to reduce a patient's susceptibility to malaria by a dose-dependent manner and the patient that has the homozygous HbSS is more resistant to malaria infection than the patient that is more heterozygous HbSA. Although, this is a double-edge sword type quality sickle cell is a deadly disease that is not transmissible, but hereditary and affects various cultures of people. Sickle cell anemia is the most frequent genetic disorder of the African American community with an infection rate of one per 375 African Americans in the United States. The affliction percentage of African Americans with sickle cell anemia is 0.15% and 1/12th of Americans with African descent possess the heterozygous sickle cell trait. Sickle cell anemia is prevalent in other ethnic groups and cultures also such people from the Mediterranean (France, Spain, Italy, Greece, Portugal, Turkey, Syria, Lebanon, Israel, Egypt, Libya, Algeria, Morocco, Tunisia), the Arabian Peninsula (Jordan, Iraq, Kuwait, Bahrain, Qatar, United Arab Emirates, Oman, Yemen, and Saudi Arabia), the Indian continent, the Caribbean, South and Central America (Lonergan, 2001). It was reported that newborn screening programs that were in 41 states, including the Washington D.C., detected sickle cell anemia using hemoglobin electrophoresis, isoelectric focusing, the high-performance chromatography, and DNA analysis in the beginning of newborn screening. Sickledex was the previous premier newborn screen technology, but because it only detects HbSS it might have missed other beta globin variants (e.g. HbSC) that can cause long term complications (Lonergan, 2001). The acute, painful vaso-occlusive crises are the most frequent and the earliest clinical manifestations of sickle cell anemia because half of all sickle cell anemia patients have possibly experience an acute pain crisis by the age of 5 unless in some extreme cases of mortality. The pain usually can be described as pain from the bones, but crises can involve any selection of organs. The vasooclusion pain crises occur in newborn children as dactylitis and that is described as a painful swelling of the hands, fingers, feet, and toes. Other clinical manifestations of sickle cell anemia in the long term include osteomyelitis, osteonecrosis, splenic infarction, splenic sequestration, acute chest syndrome, stroke, papillary necrosis, priapism, extreme hematopoiesis, and renal insufficiency (Lonergan, 2001).

Treatments & Recovery: Common and frequent treatments of sickle cell anemia consists of blood and bone marrow transfusion along with complication-specific therapy (e.g. administration of antibiotics for pneumonia), but transfusion are decisively given on the as-needed basis for numerous sickle cell anemia complications (Lonergan, 2001). This could be influenced due to the level of clinical care resources, quality of medical insurance, and condition of the patient. For the risk of stroke, there are monthly maintenance transfusions. A great example of this includes the transcranial Doppler Screening. The methods of transfusion must accomplish the 2 very important goals of 'reducing the amount of HbSS in the patient' and 'the maintaining of healthy therapeutic levels of the normal hemoglobin (HbA) (Lonergan, 2001)'.

With the maintenance transfusion, medical teams want to keep the total normal hemoglobin (HbA) concentration at 12 grams per deciliter and the HbSS concentration as 30% or less. Thankfully, maintenance transfusions have been able to significantly reduce the critical risks of first and recurrent stroke, but transfusions carry the risk of infection. Infection can bring alloimmunization and full body iron overload. Other therapies deferoxamine injections, but they can be extremely painful, they can bring on infection, and compliance from patients has been suboptimal due to patient complaints (Lonergan, 2001). The other way to reduce the amount of HbSS is transforming the nature of the hemoglobin that is produced in patient bone marrow. Medical professionals can achieve this with bone marrow and stem cell transplantation. Bone marrow and stem cell transplants come from umbilical cord blood are essential for the mitigation of sickle cell anemia. In each transplantation strategy, the medical professionals repopulate the native bone marrow with normal untransformed stem cells and/or bone marrow cells. The normal stem cells do not have to match the recipient human leukocyte antigen, but the bone marrow cells must have matching human leukocyte antigens. The positive end result of this transplantation is the production of non-Hb S-containing red blood cells. Medical practitioners have recognized that bone marrow transplantation should be done before a significant complication occurs (e.g. stroke), but medical professionals have a difficult time predicting the severity of disease in infants and early-aged children. The result of this is that there is no universal established transplantation criteria.

TABLE 1. Descriptive Statistics of Environmental Factors

Variable	Mean	Standard Deviation	Minimum	Percentile 25	50	75	Maximum
Air pollutants							
CO (μg/m³)	744.6	295.5	185.2	515.1	696.9	929.7	2716.2
NO_2 (μg/m³)	40.7	13.6	10.6	30.5	39.5	49.9	130.6
O_3 (μg/m³)	43.7	20.9	1.1	28.3	44.1	57.6	134.5
SO_2 (μg/m³)	3.8	3.5	0.0	1.31	2.8	5.2	30.6
PM_{10} (μg/m³)	27.7	12.5	6.5	19.5	24.8	32.6	138.1
$PM_{2.5}$ (μg/m³)	19.3	11.2	4.3	11.9	16.4	23.1	130.1
Meteorological variables							
Daily rainfall (mm)	1.7	3.4	0.0	0.0	0.1	1.7	35.5
Daily minimal temperature (°C)	7.9	5.9	−11.8	3.5	8.3	12.7	21.9
Daily maximal temperature (°C)	15.9	7.8	−4.3	10.0	16.4	21.9	36.8
Daily mean temperature (°C)	11.7	6.7	−6.1	6.6	12.1	17.0	28.1
Daily temperature range (°C)	8.0	3.7	0.7	5.2	7.6	10.7	19.7
Day-to-day mean temperature change (°C)	0.0	2.1	−8.8	−1.3	0.1	1.4	8.6
Daily mean wind speed (m/s)	3.5	1.4	0.7	2.5	3.2	4.2	10.1
Daily maximal wind speed (m/s)	10.9	3.6	3.6	8.3	10.3	12.8	31.9
Daily relative humidity (%)	75.8	11.6	38.9	67.6	77.4	84.9	97.9
Daily bright sunshine (%)	36.5	31.2	0.0	6.7	30.2	63.8	96.5

CO = carbon monoxide, NO_2 = nitrogen dioxide, O_3 = ozone, PM_{10} = atmospheric particulate matters with aerodyamic diameter smaller than 10 μm, $PM_{2.5}$ = atmospheric particulate matters with aerodyamic diameter smaller than 2.5 μm, SO_2 = sulfur dioxide.

Figure 1. Descriptive Statistics of Environmental Factors

TABLE 2. Matrix of Correlation Coefficients Between Environmental Factors

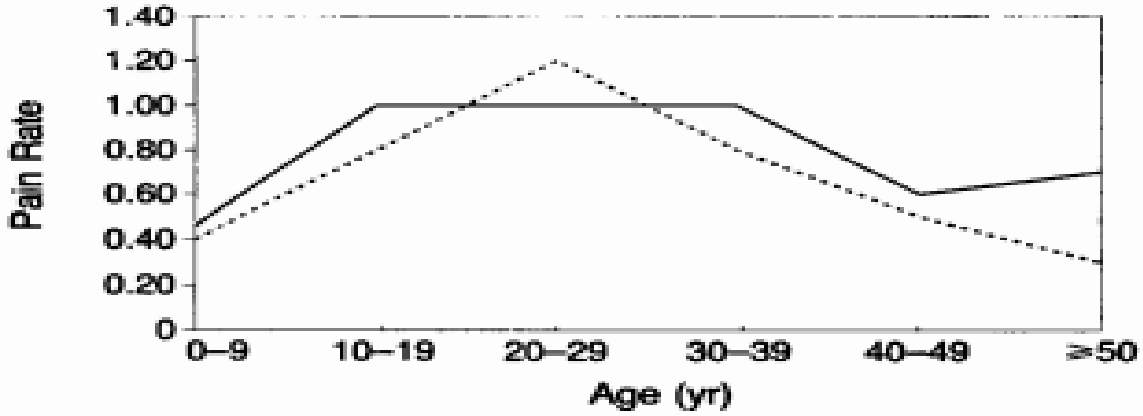
	CO	NO_2	O_3	SO_2	PM_{10}	PM_{25}	Rain	$Temp_{min}$	$Temp_{max}$	$Temp_{mean}$	$Temp_{range}$	$Wind_{mean}$	$Wind_{max}$	Hum	Sun	$Temp_{change}$	Storm
CO																	
NO_2	0.41*																
O_3	−0.26*	−0.43*															
SO_2	0.64*	0.58*	−0.38*														
PM_{10}	0.25*	0.49*	−0.17*	0.23*													
PM_{25}	0.29*	0.51*	−0.26*	0.27*	0.96*												
Rain	−0.11*	−0.08*	0.07	−0.11*	−0.22*	−0.18*											
$Temp_{min}$	−0.23*	−0.41*	0.55*	−0.46*	−0.26*	−0.34*	0.12*										
$Temp_{max}$	−0.16*	−0.32*	0.62*	−0.41*	−0.08	−0.20*	0.02*	0.89*									
$Temp_{mean}$	−0.19*	−0.37*	0.61*	−0.44*	−0.16*	−0.27*	0.05*	0.95*	0.98*								
$Temp_{range}$	0.03	−0.01†	0.42*	−0.11*	0.24*	0.12*	−0.15*	0.27*	0.68*	0.55*							
$Wind_{mean}$	−0.33*	−0.24*	0.08*	−0.10*	−0.40*	−0.39*	0.22*	−0.02	−0.17*	−0.11*	−0.32*						
$Wind_{max}$	−0.35*	−0.26*	0.19*	−0.19*	−0.41*	−0.43*	0.34*	0.10*	−0.01	0.03†	−0.19*	0.88*					
Hum	0.20*	0.18*	−0.59*	0.18*	−0.09*	0.05	0.26*	−0.36*	−0.61*	−0.53*	−0.71*	0.07*	0.01†				
Sun	0.04	0.02	0.27*	−0.04	0.28*	0.18*	−0.29*	0.07*	0.40*	0.27*	0.73*	−0.24*	−0.21*	−0.69*			
$Temp_{change}$	0.07*	0.12*	−0.13*	0.12*	0.08*	0.06*	−0.06*	0.02†	0.18*	0.15*	0.35*	−0.04*	−0.06*	−0.13*	0.08*		
Storm	−0.12	−0.24	0.25†	−0.19*	−0.12*	−0.14*	0.03	0.31*	0.30*	0.31*	0.13*	−0.01	0.05	−0.15	0.03	−0.04*	

* Correlation is significant at the 0.01 level.
† Correlation is significant at the 0.05 level.
CO = carbon monoxide, Hum = daily relative humidity, NO_2 = nitrogen dioxide, O_3 = ozone, PM_{10} = atmospheric particulate matters with aerodyamic diameter smaller than 10 μm, $PM_{2.5}$ = atmo-atmospheric particulate matters with aerodyamic diameter smaller than 2.5 μm, Rain = daily rainfall, SO_2 = sulfur dioxide, Storm = occurrence of a storm during the 7 preceding days, Sun = daily bright sunshine, $Temp_{max}$ = daily maximal temperature, $Temp_{mean}$ = daily mean temperature, $Temp_{min}$ = daily minimal temperature, $Temp_{range}$ = daily temperature range, $Wind_{max}$ = daily maximal wind speed, $Wind_{mean}$ = daily mean wind speed.

Table 2. Distribution of Pain Rates among Patients with Sickle Cell Anemia, According to Age.

Pain Rate*	Age (yr) 0–9	10–19	20–29	30–39	40–49	≥50
	% of patients					
r = 0	46	32	27	39	39	39
0<r<1	42	40	36	32	46	46
1≤r<3	11	20	25	21	13	12
3≤r<6	1	6	9	6	2	4
6≤r<10	<1	1	1	2	0	0
r≥10	0	0	<1	0	0	0
No. of patients	1093	635	424	173	61	26

*r denotes the number of episodes of pain per patient-year.



Females	527	336	242	97	38	16
Males	566	299	182	76	23	10

Figure 2. Age-Specific Pain Rates (Episodes per Patient-Year) among Male (Dashed Line) and Female (Solid Line) Patients with Sickle Cell Anemia.

Table 3. Trends in the Average Pain Rate in Individual Patients with Sickle Cell Anemia.

Age at Entry (yr)	No. of Patients*	Pain Rate for First 3 Yr†	Mean Difference‡	t§	P Value
0–4	272	0.40	0.13	3.20	0.002
5–9	223	0.56	0.16	2.83	0.005
10–14	196	0.69	0.39	3.95	0.0001
15–19	157	0.91	0.31	2.95	0.004
20–24	132	0.91	0.17	1.90	0.06
25–29	100	1.21	−0.24	−1.74	0.84
30–34	64	1.11	−0.26	−1.88	0.07
35–39	22	0.80	0.19	1.04	0.31
40–44	27	0.73	−0.04	−0.44	0.66
45–49	8	0.67	−0.30	−0.70	0.51

*Patients with at least six years of follow-up. †Number of episodes per patient-year.
‡Average difference in patient's pain rate, obtained by subtracting the rate during the first three years of observation from the rate during the next three years (or more) of observation.
§Value from two-sided t-test when mean difference = 0.

Table 5. Summary of Poisson Model for Pain Rate in Sickle Cell Anemia.

Variable	Parameter Estimate*	Standard Error	Chi-Square (df)	P Value
Intercept	−2.3190	0.8378		
Age (yr)				
5–9	0	—	16.47 (5)	0.006
10–19	0.3631	0.1399		
20–29	0.5729	0.1703		
30–39	0.3785	0.2109		
40–49	−0.0973	0.2994		
≥50	−0.1641	0.5142		
Fetal hemoglobin level, squared	−0.0032	0.0008	16.57 (1)	<0.001
Hematocrit	0.0860	0.0158	29.59 (1)	<0.001
Sex				
Female	0	—		
Male	−0.3044	0.1036	8.70 (1)	0.003

*The parameter estimates can be used to calculate the predicted average pain rate (episodes per year) for any group of patients in the standard reference clinic with certain defined variables. The model equation is pain rate = exp[−2.3190 + age-group estimate − 0.0032 (fetal hemoglobin)^2 + 0.086 (hematocrit) − 0.3044 (if males)].

Hydroxyurea is the only FDA-approved drug that can mitigate the progress of sickle cell anemia. The administration of hydroxyurea inducts the fetal hemoglobin (HbF) by the patient bone marrow and in turn reduces the production of HbSS containing red blood cells. Hydroxyurea is a cytotoxic agent and increases the production of HbF by replacing some of the abnormal beta globin chains. This results in the lowering of the relative amount of HbSS and hydroxyurea itself inhibits endothelial neutrophil production and can mitigate sickle cell anemia symptoms and statuses (pain crises, length of stay in hospital, transfusion requirements, and acute chest syndrome). It is a great thing that hydroxyurea is commonly well tolerated, but mutagenicity of sickle cell can occur (Lonergan, 2001). The lifespan of sickle cell patients has greatly increased and the quality of life has improved from the past 2 decades. From 1968 to 1992, the mortality rate of black children with sickle cell anemia have decreased by 41% (1 - 4 years old), 47% decrease (5 - 9 years old), and 53% decrease (10 - 14 years old). The median survival of sickle cell patients in the United States is 40 to 50 years. The main cause of sickle cell anemia death is acute chest syndrome (Lonergan, 2001). Acute chest syndrome is any vaso-occlusive crisis (obstruction of the blood vessels by sickled red blood cells) with the pulmonary cardiovascular system. The main determinant of survival for adolescent patients growing into adulthood patients is the end-organ damage to the lungs and kidneys. However, morbidity and mortality rates are highest in newborns, infants, and young children. Performed studies reveal that the first 10 years of life that infection, like pneumonia and influenza, is the most common cause of death only to be followed by sequestration syndrome and cerebrovascular accident. The three main indicators of an adverse sickle cell reaction were revealed to be dactylitis (< 6 months of age), severe anemia (hemoglobin concentration < 7 grams per deciliter), and leukocytosis with no additional infection (Lonergan, 2001).

Gene Therapy is another treatment avenue that is gaining ground especially with its progress in 2019. According to Sickle Cell Disease News, researchers are currently working to treat sickle cell anemia using gene therapy and two strategies have been formulated. Both of the strategies involve genetically altering the genes of the patient's very own hematopoietic stem cells because the hematopoietic stem cells are created to produce red blood cells and other types of blood cells in myeloid and lymphoid cell lines (Walker, 2019). The hematopoietic stem cells are naturally found in the bone marrow. The first strategy will have some of the patient's hematopoietic stem cells removed, the mutated HBB gene located and removed with a healthy-proper copy of the gene, and then the newly repaired cells will be transplanted back into the patient. Viral Vector Delivery or using harmless viruses as a transporter, will be utilized to deliver the gene to the cells. In theory the newly repaired hematopoietic stem cells should be able to repopulate and re-engineer the bone marrow to start producing more healthy red blood cells (Walker, 2019). The second strategy focuses on genetically altering another gene in the patient's hematopoietic stem cells to help them increase and enhance the product of fetal hemoglobin. Fetal hemoglobin is produced in recently birthed babies (< 6 months) and human embryos. Fetal hemoglobin can negate the sickling or mishapening of the healthy red blood cells in patients with sickle cell anemia, but most people really produce a very tiny amount of it after their time being an infant. Researchers try to increase the production of fetal hemoglobin in the stem cells by using a highly specific enzyme (e.g. SfiI restriction enzyme) to cut the cell's DNA in the activity area where the gene that suppresses fetal hemoglobin is located. After the modified stem cells repress its DNA, the gene will no longer work and more fetal hemoglobin can be produced (Walker, 2019). There are at least 12 clinical trials that are studying gene therapy and creating ways to treat sickle cell anemia and potential 9 of the trials are still recruiting participants. The trials designated NCT02186418, NCT03282656, NCT02247843, and NCT02140554 are coordinating their research efforts to investigate the efficacy and safety of using gene therapy to replace the mutated HBB gene with the healthy HBB gene. These trials would be following the first gene therapy strategy mentioned above. These trials are in Phase 2 and are recruiting children and adults in the United States and Jamaica (Walker, 2019). The trials designated NCT02193191, NCT02989701, and NCT03226691 are investigating the dual therapeutic use of Mozobil, a medication that can mobilize hematopoietic stem cells for collecting peripheral blood and autologous transplantation in patients with Non-Hodgkin's lymphoma (NHL) or Multiple Myeloma (MM)[4]. In theory Mozobil, could help sickle cell anemia patients to increase the production of healthy hematopoietic stem cells to be used for gene therapy. All of the trials are in Phase 2 and are recruiting participants in the United States only. The trial designated NCT00669305's goal is to recruit bone marrow donations from sickle cell anemia patients to be used in laboratory research to develop new and improved gene therapy techniques. This trial is specifically recruiting for donors in the state of Tennessee. The trial designated NCT00012545 will be examines the best methods of how to retrieve, process and store umbilical cord blood from babies that have and do not have sickle cell anemia. The cord blood from babies has abundant stem cells with medicinal properties that have the potential to be used in developing gene therapy treatments for sickle cell anemia. The trial is opening recruitment for pregnant women in Maryland who have infants that could or could not have the risk of developing sickle cell anemia (Walker, 2019). A European trial designated NCT02151526 is still currently active in working to investigate the efficacy of gene therapy for seven patients. The research plan of this clinical trial is to insert a gene in the patient's stem cells that can produce therapeutic hemoglobin that can function similar to fetal hemoglobin. The clinical trial did generate a case study in March 2017 that described how the approach was safe and did suppress the activity of sickle cell anemia (Walker, 2019).

Levels of Primary, Secondary, and Tertiary Prevention

Primary Prevention

Genetic Counseling Education & Carrier Testing: There are many social services and psychologic support activities that maintain the health of adult sickle cell patients. These activities and resources are usually given to social workers and mental health professionals because there is a stigma about sickle cell anemia that you are either cursed or that you caught it from someone else possibly through sex. The stress of dealing with sickle cell anemia can be great you a sickle cell patient will not be as normal as everyone else. Sickle cell patients will have to go through a lot of medical checkups after procedures, they have to take medication almost daily, patients won't be able to do certain jobs that require strenuous physical feats like going up high altitudes or being in very cold environments, patients deal with various levels and frequencies of pain that could possibly kill them at any time, and if they want to start a family

the patient will have to find a significant other that does not have sickle cell anemia or is a carrier for the disease. The mental health workers can be very helpful in managing and even mastering the psychiatric problems that could come with having sickle cell anemia such as loneliness, depression, and hopeless through teaching coping skills and effective mechanisms dealing with the cognitive and behavioral combat of pain. Hematologists can provide carrier screening to determine which allele variant of the sickle that a person has and can follow up with mainly food and medicines that would be helpful in mitigating the levels of pain if a person has inherited sickle cell anemia. There have been many recommendations of screening programs and education and counseling programs to work together as best as possible to inform the community of what people can do if they determine that they, relatives, friends, or their children could have the trait or the disease. The early counseling process for parents of newborns that have sickle cell disease can involve discussions on secondary strategies for prevention like penicillin therapy, but the main agenda is for any genetic counseling meeting is the communicating of recurring risks and reproductive options.

Other forms of sub-primary prevention if a person only has the sickle cell trait is that person could exercise and eat a healthy and rich diet of high-calcium and iron foods to maintain good blood pressure and blood cell count, continue to consume the right amounts of vitamins and minerals, continue to stay hydrated, practice safe sex, and continue to ask questions to get educated and educate others. In 1972, the 92nd Congress of the United States drafted and passed the "National Sickle Cell Control Act. This action bill called for various grant support for voluntary screening and counseling programs. The programs were specifically provided first to people who are entering their child creating years and secondly, to children under the age of 7. A great deal of funding for sickle cell research, counseling, and education programs become available and it helped created newborn screening programs as well as the Prophylactic Penicillin Study. Due to this funding by the U.S. Congress, the Funding for the Cooperative Study of Sickle Cell Disease was created and it provided much of the support data for sickle cell tertiary prevention strategies. There are other organizations and institutions that have contributed primary prevention methods such as National Institutes of Health, the Centers for Disease Control and Prevention, the Health Resources and Services Administration, and the Agency for Health Care Policy and Research (Reid, 2002).

Secondary Prevention: Newborn screening is very important because it is the representation of the launching point for secondary prevention strategies. The genetic screening test for sickle cell anemia is called the Sickle Cell Test. The Sickle Cell Test is a simple blood test that can determine if a person has sickle cell disease or sickle cell trait. Normally the sickle cell test is part of the routine screening performed on a newborn baby, but the test can be used for adults.

The diagnosis of sickle cell disease or sickle cell trait in a child will reveal and open a wide window for revealing the carrier status of the child's parents which they probably did not know beforehand. This can also lead to some social issues that genetic counseling and can fix. Prenatal hemoglobinopathies have been highly recommended by many medical organizations and is very feasible. Hemoglobinopathy is a disorder where the structure of the hemoglobin is abnormal. Hemoglobinopathy is the most common inherited disorder in the world (Cober, 2010). Prenatal hemoglobinopathies help determine if a newborn baby has any traces of hemoglobinopathy. There have been some ethical, legal, and social controversies regarding the choice to use sickle cell carrier screening and the usage of those screening results to make reproductive decisions. There are many results that point to the medical benefits and cost-effectiveness of various genetic screenings, especially in certain populations. There was a study of U.S. death certificates for the year range of 1968 - 1992, researchers found that mortality among black children of ages 1-4 that had sickle cell disease had actually declined. This life-extending trend occurred at the same time as the establishment of newborn screening programs along with more extensive and versatile medical care and parental education, widespread acceptance of penicillin prophylaxis, and new immunizations (Cober, 2010). The next secondary prevention option is to use penicillin prophylaxis. According to the American Academy of Pediatrics, penicillin prophylaxis is recommended to be used to prevent pneumococcal infection, which sickle cell anemia newborns (under age 5) are at risk for[6]. It has been proven to act better against pneumococcal infection than the s. pneumococcal vaccine and has an extended length of activity longer the vaccine. However, the pneumococcal bacteria strain has been documented to develop a small resistance to the medicine (Cober, 2010).

Tertiary Prevention: An important global research initiative, called the "Global Epidemiology of Sickle Haemoglobin in Neonates: A Contemporary Geostatistical Model-Based Map and Population Estimates", was started to create reliable estimates of populations affected by sickle cell anemia in newborns in order to guide efficient allocation of public health resources in 2013. The used a created database of various sickle haemoglobin surveys from online bibliographic searches and from that data researchers created a contemporary global map of the HbS allele frequency distribution with a Bayesian geostatistical model. Surveys that had any selection bias like ethnicity of health status were excluded and any remaining surveys were judged to be retained as representations of local populations if the sample size and number of disease carriers (asymptomatic) and disease sufferers (SS = Sickle Cell Anemia) if they were reported and could be georeferenced to the district level. The input data for this model also included geographic coordinates or the latitude-longitude in decimal degrees as well as the number of HbS and non-HbS alleles in the population samples. The reason that the sickle haemoglobin (HbS) mutation was targeted was due to lack of frequency distribution data and because it is the most common pathological haemoglobin mutation worldwide. The HbS mutation is an alternate variation of the HbA phenotype that represents the normal adult haemoglobin and is inherited from both parents. This mutation can lead to complications and without the proper financial and medical resources children usually end up dying at very young ages. There was a total of 1,211 spatially unique data points from the 435 references that matched all of the required inclusion criteria. 619 of the data points (51%) of the HbS mutation was located in the African continent, 23% was located in the Asian continent, 17% was located in the Americas, 9% was located in Europe and less than 1% was located in Oceania. The researchers also tested and analyzed for the absence of the HbS mutation in the world and this was recorded for 292 data points. 117 for Asia, 86 in Africa, 69 in the Americas, 17 in Europe, and 3 in Oceania. 9,032,377 individuals were counted from the selected surveys total.

The continent of Africa had the highest frequency of the HbS mutations, but Africa had the second highest absence of the HbS gene (Piel, 2013). This finding is very interesting and could mean that because of the new ways of transportation as well as the new laws of immigration, cultural traditions, and citizenship rights that the HbS gene is in various nationalities that are coming to and from the continent of Africa. There is an increasing burden of sickle cell anemia and other haemoglobin disorders that will increase in the coming feature making it harder to track the diseases to prevent them. Further examples of tertiary levels of prevention include hydroxyurea therapy, prophylactic transfusions to prevent stroke recurrence, daily folic acid supplementation for the prevention of megaloblastic anemia, and outpatient administration of analgesics and hydration of pain. There are further actions to cure sickle cell disease includes bone marrow transplantation and gene therapy, but due to these options being in their developmental stages and being somewhat expensive, their do not yet carry adequate medical impact of public health and society. The hydroxyurea therapy so far is the best choice of drug to use to mitigate the effects of sickle cell anemia (Olney, 1999).

Epidemiological Model Analysis of Risk Factors: Wheel Model Force Field Analysis

Categories: Environmental Factors, Behaviors or Lifestyles, Genetic Factors, Health Care Services. The Epidemiological Model that has the best accuracy and tools to tailor the variability and reserved functions of Sickle Cell Anemia is the Force Field Model. In 1974, the Force Field Model was developed by Henrik Blum and the model specializes in analyzing disease occurrence and the state of a community's health. Sickle cell anemia has doesn't just have a community, but it has a diaspora of hosts and cultures, mostly African & African American, but also Asian (Chinese, Indian, Thai) and Middle Eastern. The Force Field Model has four categories and they are Environmental Factors, Behavior/Lifestyles, Genetic Factors, and Health Care Services. Sickle Cell Anemia for the most part is 90% genetic because it is a hereditary disease, but surprisingly enough some of the 10% of the disease process and progression is due to a mix of Environmental Factors, Behavior, and Health Care Services. Henrik Blum might have been empathetic, yet effort performance driven when he made the following statement about health saying that:

> "Health is a state of being in which individuals do the best with the capacities they have, and act in ways that maximize their capacities." The community plagued by Sickle Cell Anemia, whether they know it or not, resonate with this statement quite profoundly.

Lifestyle Factors: There are little to no current research studies or data that resoundingly provide any lifestyle factors that cause or create Sickle Cell Anemia. There are only lifestyle factors that sickle cell patients have to change and manage when it comes to preventing and mitigating sickle cell crises. One of lifestyle and medical care changes that people with sickle cell anemia must adjust to is staying on top and ahead of their healthcare service maintenance or more simply put, making sure that there are going to doctor's appointments, getting immunization shots, and taking the necessary prescribed dietary supplements. If a newborn child is diagnosed with sickle cell anemia, then for the first 2 years of newborn's life, healthcare and doctor's appointment visits should be scheduled concurrently for needed immunizations. For the much older patients, particularly if they are doing well, their appointments and healthcare visits occur semi-annually[5]. Particular immunizations that sickle cell children must have are the immunizations against the hepatitis B virus and the polyvalent pneumococcal vaccines are 2 years old and the seasonal influenza vaccine when recommended by the American Academy of Pediatrics or Family Practice[5]. Sickle cell anemia can weaken the blood system due to irregular shaped 'sickle' cells and this of course cannot carry enough nutrients like oxygen to boost the immune system to help adequately fight various viruses and other diseases.

Another change that must occur in sickle cell patients is routine dietary health care counseling. For newborn sickle cell children, it is recommended that mothers breastfeed their children for natural vitamins and nutrients such as Vitamin D, although an alternate option is iron-fortified formulas[5]. Vitamin D deficiency is a huge issue in children with sickle cell disease. Another huge vitamin deficiency in sickle cell anemia patients, particularly in the African-American community is the deficiency of iron in the blood. The deficiency of iron in the blood is very important for sickle cell anemia patients because this deficiency can promote the occurrence of alpha thalassemia. Alpha thalassemia is any blood disorder that reduces the production of hemoglobin which is protein in red blood cells that carries oxygen to the rest of the cells throughout the body. Alpha thalassemia can be difficult to diagnose due to microcytosis providing alpha thalassemia cover in the form of making the red blood cells much smaller and harder to count than usual. This could cause some complications due to the doctor providing the incorrect dose of medication or supplement to bring the red blood cell count back to normal levels. Although iron supplements are a good alternative, a patient should not take iron supplements unless their doctor documents them having reduced iron stores from specific assessments of the serum ferritin levels/serum iron binding capacity. Therefore, it would be much better and easier to eat foods that provide rich amounts of iron such as beans, dried fruit, yogurt, milk, orange juice, leafy green vegetables, soymilk, nut butters, smoothies and various yogurt. Finally, in regards to dietary health counseling, especially for newborns, children, and even the elderly, special attention and regulation should be paid to the diet if education, unmet economic needs, or cultural patterns place the patient at risk of dietary deficiencies (Reid, 2002). Dental care is another aspect that changes for sickle cell patients. Sickle cell anemia can degrade the bone minerals and nutrients in the teeth such as the molars, canines, and the tooth enamel. Therefore, it is recommended by healthcare professionals that supplemental fluoride is given topically in vitamins or possibly in drinking water to be provided based on a vitamin schedule. Thankfully, cleaning and dental fillings do not require special care for sickle cell anemia patients, but any other dental operation procedures (e.g. extractions & root canal therapy) must be followed with standard rheumatic fever antibiotic prophylaxis for the lessening of bacteremia/sepsis risks. What's even more critical is that if general anesthesia must be used, a child with sickle cell anemia and potentially anyone other patient, must be or should be ready to be hospitalized, and preoperative transfusion might need to be considered for any extensive surgical operations[5]. Finally, other healthcare aspects that sickle cell anemia patients must be checked on & discussed about in thorough detail includes hearing and vision (ocular complications of sickle cell disease), skin (risk of

tuberculosis), the potential deadly effects from the use of drugs (tobacco & alcohol), safe sex practices and abstinence (if sexually active the usage of condoms is advised to protect against sexually transmitted disease like HIV), organ dysfunction, stunted growth, physical activity frequency and level (strenuous exercise is not always recommended), and potential pregnancy (ladies that have sickle cell anemia need to be provided with safe, non-specific contraindication birth control). Adolescent sickle cell patients have a social aspect that they must deal with due to having sickle cell anemia. Having sickle cell anemia can be very difficult and sometimes be misunderstood by other people. There are a multitude of social problems that adolescent sickle cell patients face such as having to miss school and social events due to appointments, not feeling well or not physically suited to perform a certain task, lack of motivation because of feeling sick and feeling no support. Healthcare practitioners that treat adolescent patients with sickle cell anemia must know the local resources available for assistance such as motivating and guiding parents and patients with peer support groups, online support help, (great support for patients that can't leave home), stress reduction techniques (breathing and meditation are helpful), cognitive-behavioral therapy (coping skills to deal with pain), vocational and academic counseling (letting teachers and officials how to handle any academic and medical difficulties that could occur due to sickle cell), recreational travel (high altitudes and cold weather can painfully injure sickle cell patients) (Reid, 2002). The transition for sickle cell patients from adolescence to adulthood can be very challenging because since there are not many abundant sickle cell anemia healthcare professionals, a patient sticks with a certain group of pediatric healthcare professionals from childbirth and will have to switch to adult healthcare professionals when they come of age (Reid, 2002).

Medical Care Factors: The biggest challenge for medical care for sickle cell anemia patients is the implementation of transition from adolescence to adulthood. There are various members of a transition team ranging from physicians, nurses, physician assistants, and social service workers at the adolescent/pediatric stage and the adulthood stage. A great aspect is that adolescents have known their medical team of providers possibly for their entire lives and when they become adults they will have to leave their previous caretakers, meet and learn to interact with their new caretakers. Another challenge in the transition for medical care for sickle cell patients is the transfer of medical records and documentation. Written medical records and change so it is important for medical staff, parents, and even patients to say verbally repeat medical records on supplementation/medication, blood pressure and blood cell counts, and tests results. Furthermore, having the initial meeting and following up between the adolescent medical team and the adulthood medical team of the sickle cell anemia patient is very important if something needs to be re-verified, to give progress reports on the patient, or to ask questions.

The hierarchy of a Sickle Cell Anemia medical care-team, particularly for adolescents, has the pediatricians as the medical head decision-makers and that hematologists have the consulting duties. All children have to see a pediatrician for developmental check ups with routine immunization. The pediatrician is usually the main point of medical contact, which is why the pediatrician is the head medical decision maker. Any immunization or supplementation decision however, must be consulted and signed off by the hematologist because of how the blood cells can be affected[5]. When the patient reaches age 18 and if they are considered healthy and adept, the patient would more often than not consult the hematologist as the chief medical decision maker and adviser, but of course this is not always the case (Reid, 2002). At the legal adulthood age of 18, a patient might not be ready to transition to an adult care doctor because of delayed neurocognitive development due to cerebrovascular injury or because of a serious complication (e.g., acute chest compression) might not be ready to transition to an adult care health professional. In fact, the choice of the young adult patients to go to medical checkups when they feel healthy, to remember to take their medication daily, and the desire to be independent is a challenge in itself. Research has shown that 'healthy' young adults with mild SCD have a mild tendency to skip follow-up appointments with their medical specialists that can prevent complications of SCD.

By continually skipping these appointments, symptoms and complications can arise such as asymptomatic retinal blood vessel proliferation leading to ocular hemorrhage (Reid, 2002). Social service workers are vital to the decision of whether a patient should still continue to stick with pediatric care or transition to adult care due to having the most continuous contact between the healthcare professionals, the patient, and the patient's family. Social service works can make authoritative judgments on how families react to sickle cell complications and the psychosocial problems like anxiety and depression. The social service workers can provide counsel in advance before the patient and family transitions to adult care. The inner workings of a Sickle Cell Anemia/Disease Department is that the pediatric medicine and adult medicine departments must be able to balance out one another. If one side is very weak or if one side is not there then one side will have to find a way to overcompensate and stretch themselves. Yet by only having one be strong and not the other, the patient's full needs will not be met if the patient chooses to not stick to the medical regimen. To add on to this obstacle, there are not enough specialized health care professionals with the comprehensive knowledge and expertise to care for people with sickle cell anemia (State of Sickle Cell Disease, 2016).

There is a huge knowledge gap for hematologists and primary care, but also among other groups such as clinicians that provide outpatient and hospital based care, especially for adults. According to a national survey, 20.4% of family physicians reported that they felt confident and comfortable treating people with sickle cell disease and 69.4% of family physicians reported that clinical decision support tools would be useful in assisting treatment decisions for individuals with sickle cell disease (American Society of Hematology, 2016). These statistics are probably worse for treating adult Sickle Cell Disease patients. It is a fact that some people with sickle cell disease rely exclusively on the hospital or emergency department for care, due to a lack of increase in qualified sickle cell disease providers, and adults have higher rates of emergency room admissions for sickle cell disease that children. The final challenge regarding the medical care aspect is the money to pay for the care of Sickle Cell Anemia Disease patients. Research has shown that the children with the disease that come from heterozygous parents have insurance paying for their medical care. With sickle cell children, mainly self-limited painful events force them to be hospitalized on an

emergency basis. In other words, if you a family has insurance then it is easier to pay for a sickle cell child.

The case for the sickle cell adult is different. Sickle cell adults have progressive organ dysfunction and damage which increases the time they have to take away from work to get better, but on the downside, these adults cannot make enough money due to lesser hours worked and they cannot pay for insurance plans backed by medical insurance firms or governmental assistance. To add to this problem, some of the governmental and insurance programs don't have enough funds to pay for the medical services for adult patients either because they run out of money or because their programs have an age limit cutoff for funds (Reid, 2002).

Environmental Factors: Although Sickle Cell Anemia Disease is caused through genetic heredity means, researchers have found a potential correlation between the quality of the weather, air pollution rates, and the progression of daily emergency room admissions of sickle cell patients. A team of dedicated French researchers performed an 8 year retrospective epidemiological study evaluating the influence of air pollution and climatic factors on emergency hospital admissions (EHA) in sickle cell patients in 22 French university hospitals in the Paris conurbation (extended urban area). The researchers used distributed lag non-linear models to find the data that would allow them to elastically describe any simultaneous non-linear and delayed associations (Dessap *et al*., 2014).

Sickle cell disease has heavy characterization of recurrent vaso-occlusive pain crisis (VOCs) and VOCs are the most common reasons for sickle cell disease patient emergency admissions. Factors that are known or rather more suspected to promote VOC is dehydration, hypoxemia, pregnancy, infections, and surgery. Erythrocyte cell sickling has been known to be enhanced by lower temperatures and studies of cell biology and human physiology have discovered and further demonstrated a link between the skin cooling and vaso-occlusion[9]. For the 8 year study than spanned 2,922 days, a total of 17,710 emergency admission for VOC or chest disease occurred with a total of 4,436 patients affected. Figure 1 summarizes the detailed statistics for the weather conditions and air quality for the 2,922 days and Figure 2 shows the matrix of correlation coefficients between environmental factors. There were at least 265 days or 9.1% of the total study time where storms occurred and nearly all of the meteorological variables and air pollutants correlated closely with each other being less than 0.01 (Dessap *et al*., 2014).

The multivariate analysis that the research team conducted demonstrated that due to day-to-day temperature drop, increased mean wind speed and decreased carbon monoxide concentrations were independent factors that contributed to the increase of Emergency Hospital Admissions (EHA) risk. Their results did correlate with previous physiological studies that reported how seasonally colder temperatures may severely increase the pain from sickle cell disease. The study of the air pollutants in the French conurbation established that there were variations in urban air pollution and adverse health effects and that there is poorer air quality in those areas. To conclude, the increase in EHA was associated to the higher levels of toxic NO2, PM10, and PM2.5 as well as the lower levels of the beneficial CO, O3, and NO2. The CO can bind to hemoglobin with 200-fold affinity than O2 while forming carboxyhaemoglobin (HbCO). Carboxyhemoglobin (HbCO) increases the binding sites for O2 to attach to and provides better air to breathe. The inhaled CO reduces harmful symptoms of inflammation, leukocytosis, and vasoocclusion which can kill sickle cell disease patients (Dessap *et al*., 2014).

Genetic Factors

Molecular Genetic Mechanisms of Sickle Cell Anemia: Normal hemoglobin molecules have four healthy globin chains which are two alpha chains and two beta chains. When the two alpha and beta chains are normal the genotype produced is HbA. An abnormal hemoglobin is indicated due to the type of abnormality in the globin chain. The abnormal hemoglobin like HbSS is commonly the result of the abnormality in the beta chains, not the alpha chains. The beta globin chain is coded on the short arm of 'chromosome 11' and when amino acid valine is substituted for glutamic acid at the 6 spot of the beta globin chain the product result is the sickle cell Beta globin chain (HbS) (Lonergan, 2001). This is caused by a point mutation. The HbS beta globin chain, due to valine being substituted at the 6 spot, has as a negative and uncanny inclined tendency to bind with other HbS chains when it is deoxygenated. This is where the basic structural unit known as a twisted, ropelike structure composed primarily of two complete hemoglobin molecule strands. The twisted rope structure binds with the between the beta globin chains and creates the deformed sickle cell. This is where the image of the sickle cell or banana cell comes from. The process that creates the twisted ropelike structure and the deformed sickle cell is called 'polymerization (Lonergan, 2001)'.

> The polymerization process follows up with causing the nonselective increase in membrane cation permeability to sodium, potassium, magnesium, and calcium. When the time comes for these cations to enter the red blood cell down their concentration gradient, there are several cell membrane transport systems activated. The critical effect of this result is an egress of water or dehydration and the sickle cell becomes dense and deoxygenated (Lonergan, 2001).

Vitamin D Deficiency: Vitamin D is a vital nutrient for children with the homozygous SS sickle cell disease (SCD-SS), but children across a vast range of locations are deficient of it due to increased skin melanin concentrations, reduced levels of physical activity and poor vitamin D intake[10]. There is already a low bone mineral density in children with SCD, which is a further cause for concern in regards to the possible consequences of vitamin D deficiency. Sickle cell disease primarily affects Africans and African Americans and the children homozygous for the SS allele (SCD-SS) are severely affected the most. Children with SCD-SS are a risk for nutrient deficiencies because of factors such as decreased appetite, poor dietary intake, and increased resting energy expenditure. Serum 25-hydroxyvitamin D [25(OH)D] concentration is the current best indicator of vitamin D because it represents the summation of the synthesis of cutaneous vitamin D and that includes ingestion of either vitamin D-2 (ergocalciferol) or vitamin D-3 (cholecalciferol). There have been recent widespread studies that suggest that vitamin D insufficiency is quite common in the United States and that there are a wide array of vitamin D status predictors such as ethnicity, season, age, body mass index (BMI), latitude, use of dietary supplements, and milk consumption. Usually on average,

people think of people with thicker frames and a higher body mass index possibly due to heavier bones have more vitamin D in their systems, but we can't accept this for certain. This research study aimed to compare the vitamin D status of African and African American children with SCD-SS with a healthy, African-American reference group living in the same geographic area (Rovner, 2008).

The research study had a sample size of sixty-one subjects that had SCD-SS (49% female) and 89 healthy African American subjects (46% female) with similar age ranges in the same geographical area. The children that suffered from the SCD-SS had a lower BMI than the healthy children. The medium serum 25(OH)D concentrations were 15 ng/mL, which was in the standard interquartile range of 10 to 33, for SCD-SS children and the medium serum 25(OH)D concentration was 21 ng/mL, in the standard range for healthy children (High Vitamin D Deficiency in Sickle Cell Disease Children). An interesting observation was that when there when the season changed in the geographical area there were fluctuations in the serum concentrations of both groups of children. During every season change, the serum concentration was still lower in the SCD-SS children and higher in the healthy children. This was strange because 93% of the SCD-SS children has vitamin D deficiency, but 90% of the healthy children had vitamin D deficiency as well. These findings are consistent with multiple results from other locations in the United States such as Oakland, California with a latitude of 37.80 degrees North) and Philadelphia, Pennsylvania with a latitude of 39.95 degrees North). It seems that the higher the elevation a person goes whether they had sickle cell disease or not, the harder it is to get oxygen and vitamin D. Yet it seems that absorbing adequate amounts of nutrients in sickle cell disease patients is still very inept.

Pain Rate Due to Age: Acute pain episodes or 'crises' as they are called are the principal symptoms of sickle cell disease. Investigators are still trying to find the clear definitive relationship of these crises or other risk factors to absolutely determine if patients have rates of pain die prematurely and die frequently. A study was performed where researchers analyzed the natural history of sickle cell disease in 3,578 patients ranging from newborns to 66 year old adults (Platt *et al*., 1991). In the study, there were 12,290 episodes of pain recorded in 18,356 patient-years and this created some interesting statistics. There were averages of:

- episodes per patient-year in sickle cell anemia
- episode per patient-year in sickle Beta^0 thalassemia
- episode per patient-year in hemoglobin sickle cell disease combined with the sickle cell Beta^0 thalassemia combined

There were many changes in these episode statistics. 39% of the patients with sickle cell anemia experienced 0 episodes of pain, which is uncanny, but 1% of the patients with sickle cell anemia experienced more than 6 pain episodes. Another interesting statistic is that 5.2% of patients with sickle cell anemia experienced 3 to 10 pain episodes and that cohort composed 32.9 percent of the episodes. What could have been the possible variables that contributed to this system of results? Age? Ethnicity? Melanin? Vitamins? Level of Care? Availability of Care? Genetics?. According to Figure 3 and Figure 4 there are relations between the pain rate and the age of the sickle cell anemia patients (Platt *et al*., 1991). This is backed up by research that the pain episodes increase in severity as sickle cell anemia patients age, especially when it pertains to organ dysfunction. Figure 2 specifically implies that the pain rate increased as patients grew older, from 0 to 30 years, yet declined afterwards[11]. The section of patients aged 20 to 29 years old had higher pain rates than the section of patients that were ages 0 to 9, 40 to 49, exactly 50 years old, or older than 50 years old.

The researchers thought these results were misleading and they performed another cross-sectional analysis to determine whether on average, individual patients actually had worsening or improvement over time. The researchers evaluated average individual trends in the pain rate among all patients with at least 6 years of follow-up time. Figure 3 is the summarization of that data of the pain rate of those first 3 follow-up years with the last 3 follow-up years. The patients that were 20 years old or younger, the pain rate was dominantly higher during the last 3 follow-up years than the first 3 follow-up years. The patients over 20 years old, the rates during the entire 6 follow up years were not significantly different (Platt, 1991). Some interesting relationships between the pain rate and various statuses occurred. The researchers found that there was no relation between mortality and pain rate for patients that entered the study from 20 to 29 years old (Platt, 1991). This could be the case because in the age range usually a person's immune system and genetic fitness is at potential peaking point of performance. There were some risk factors that were found for the pain rate. When the researchers controlled for age, sex, and the type of clinic in the statistical analysis, they found out that all of the laboratory variables that were tested, only the hematocrit and the fetal hemoglobin levels emerged as the important risk factors for pain. This is presented by Figure 3 and an equation was even created to model this:

$$\text{Rate} = \exp [A + 0.086 (\text{hematocrit})]$$

A = statistical value correlated to a combination of the patient's age, fetal hemoglobin level, clinic, and sex. To conclude, alpha-thalassemia by itself had no effective influence on pain. If there was a slight increase in the pain rate associated with a-thalassemia, that increase in pain was aided by the slightly higher amount of hematocrit in patients with hemoglobinopathy or abnormal structures of hemoglobin.

Conclusion

Sickle cell anemia is a global health problem formally recognized by the World Health Organization, the Center for Disease Control and Prevention, the United Nations, and the National Institutes of Health. It is estimated that 120,000 to 250,000 infants that are affected every year. The most notable peoples and nationalities that are at risk for sickle cell anemia include Africans, African Americans, South & Central American, Caribbeans, Mediterreneans, Chinese, Indians, and Arabians. Infants and child patients with sickle cell anemia need greater amounts of medical monitoring and care for stroke risk and even adult patients need more medical monitoring to make sure that they are taking their treatment medication and attending every medical appointment. Based on medical data and research, there are more support programs and initiatives for child and infant patients with at least 41 states in the United States having sickle cell anemia screening programs. There are many lifestyle factors that must change

for sickle cell anemia patients including increase vitamin intake to address Vitamin D deficiency and living in clear air and non-cold temperature environments. Increased training (e.g., dealing with acute pain crises and genetic analysis) and coordinated resources (e.g., mental health support, proper dieting and exercise regimens) for medical and healthcare professionals in regards to sickle cell anemia and sickle cell disease is needed to help patients going from childhood to adulthood and especially if the patients have to change living locations. The increase of sickle cell anemia specialists in the United States and the world can definitely stop the spread of sickle cell while also creating strategies to improve the lives of patients that already have the disorder. The most common treatment for sickle cell anemia includes bone marrow transplantation. However, the biggest obstacle with the transplantation is making sure that the donor is healthy and that the patient's body can accept the bone marrow donation. The second best treatment is the FDA-approved drug known as Hydroxyurea, which increases the production of fetal hemoglobin. Penicillin Prophylaxis is an older treatment. Another route of treatment for sickle cell anemia is gene therapy where the disease causing gene is altered or a healthy copy of the mutated gene is inserted into the body. Other aspects of gene therapy treatment, particularly for sickle cell anemia includes, finding genetic and biological material to increase the production of fetal hemoglobin in patients since it can repress the sickling (blood cell misshaping). Clinical trials using gene therapy are still ongoing and have shown great therapeutic potential. Genetic Counseling and Carrier Testing are trusted primary prevention methods, Newborn Screening and Prenatal Hemoglobinopathies are reliable secondary prevention methods, and Geostatistical Model-Based Mapping to create accurate estimates of affected populations with sickle cell anemia is a rising innovative tertiary prevention method to stop sickle cell anemia for continuing to develop and cause more harm. All of the efforts to stop sickle cell anemia continues to improve the condition and increase the lifespan of patients with sickle cell anemia. More continued improvements and supportive efforts can help stop sickle cell anemia and other lethal genetic disorders all across the world.

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