

Sickle Cell Disease - A Comprehensive Study and Usage of Technology for Diagnosis

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Authors' contributions

This work was carried out in collaboration among all authors. Author SY initiated the work, designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript as the Principal Investigator (PI). Author MSV acts as Co-Principal Investigator (Co-PI) for the above work and involved in all phases of the work. Authors BPG and YHC acts as student interns for this work and involved in all phases of the work like management the analyses of the study. Author PESNKP managed the literature searches and helps the team to find the technical sources. All authors read and approved the final manuscript.

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ABSTRACT

Sickle cell is haematological disorder (haematology is a study of blood in health and diseases) which may lead to an organ damage, heart strokes and serious complications. It may also reduce human life span. Most of the sickle cells are observed in new born babies. At the start of sickle cells in human people though it's a kind of feature in tribal people but it has spread over the world. Sickle cell Symptoms are observed in human beings as episodes of pains (crisis), Vision problems, swelling of hands and Feet. Sickle Cell Disease (SCD) can harm patient's spleen (slightly pain at left Ribs). If one organ is affected in human body, then slowly it affects the entire body by spreading into Brain, Lungs, Heart, Liver, Kidneys, Joints, Eyes, Penis, Skin or Bone. This paper is aimed at

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presenting the complete details of the SCD with its properties, symptoms, signs, treatment for this disease. This is also a comprehensive study and characteristics of this disease with other similar diseases. The technological implications and usage in the field of SCD for better accuracy of identification of the disease is presented.

Keywords: Sickle Cell (SC); Sickle Cell Disease (SCD); thalassemia; image segmentation; Sickle Cell Anemia (SCA).

1. INTRODUCTION

Sickle Cell Anemia (SCA) is a one kind of abnormal blood disease which is usually called as Sickle cell Disease (SCD) or a normal Sickle Cell. In human body, blood flows through small circular shape which carries oxygen to organs where sickle cells shape are disc shape (sickle shaped cells) as shown in Fig. 1.

A normal blood cell life span is approximately 120 days. After 120 days a new blood cell is generated [1]. Sickle cell life span is 10 to 20

days [2]. This cell is an inherited disorder that affects normal hemoglobin present in the Red Blood Cells (RBC) [1,3]. The presence of sickle cell in hemoglobin leads to the formation of sickle-shaped cells that are very rigid and sticky as shown in Fig. 2. This kind of anemia may cause severe pain, necrosis and serious complications, in some cases it may lead to death.

SCD is mainly caused by a mutation in the sixth codon of the β -globin gene on chromosome 11 that leads to a single amino acid substitution [4].



Fig. 1. Visual representation of normal blood cell and sickle cell

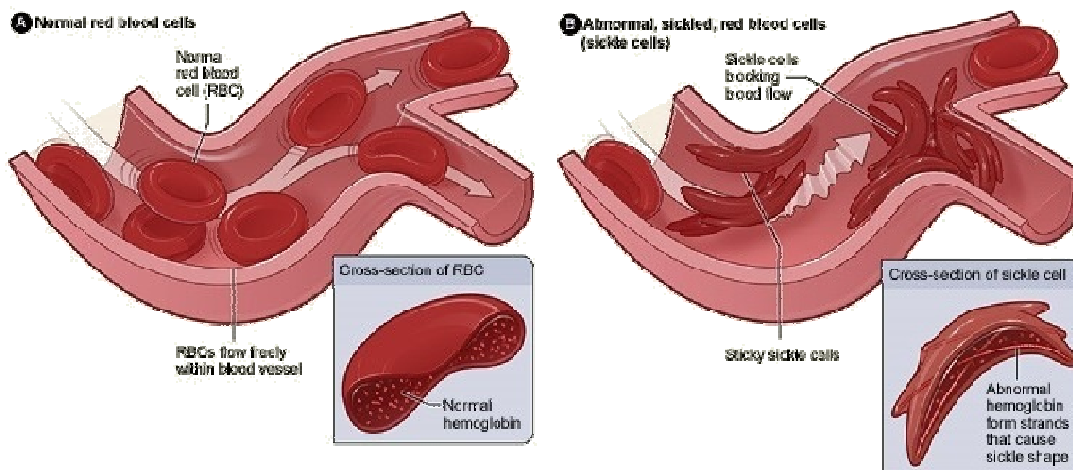


Fig. 2. Normal blood flow and sickle cell blood flow

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In above Fig. 2, we can clearly see that the normal blood flow will flow freely so it cannot cause any problem as their shape is in circular which carries oxygen to organs where sickle cell shape is sticky due to that blood flow will stop at any stage. Due to stoppage of blood flow, human beings may cause severe body pains, heart strokes etc. Sickle cell is firstly observed in the black population later it has been observed in people of other ethnic group, which include individuals from parts of the Middle East, Central India, Mediterranean Sea, especially in Italy and Greece. Treatment is available for SCD by taking Antibiotics and Blood Transfusion. The medication includes prophylactic antibiotic and immunizations are used. Along with this, certain vitamins and medicines such as folic acid and hydroxyurea can also be considered. The patients with severity of SCD are advised to go with Bone marrow transplantation which is treated as the high impacted treatment for SCD. After early diagnosis and detection, Doctors may recommend medicines or transfusions to manage complications of the disease, including pain management.

Due to the sickle shape of the blood cell and its nature of sticky, the blood cells were stopped flowing through the blood vessels and results painful episodes in patients' life. Pain management is an important phase of treatment for this disease. Patients who experience sequence of splenic sequestration may definitely require splenectomy. Bone marrow transplantation is treated as the only curative form of treatment [5].

SCD is actually very rare blood disorder in human body but now it has been observed very quiet in human hemoglobin. Sickle cell is also observed in new born babies. SCD are crescent-shaped cells which are stiff and sticky and interact with other cells. Due to sticky sickle cell in human hemoglobin it stops blood to flow in human body, if one organ is affected slowly it will be spreading entire human organs which may lead to death. To prevent this anemia type of disease, major step is to take blood transfusion for 1-2 months for normal flow of nutrition and oxygen.

When two abnormal genes causes a person with hemoglobin S, in which a person has two hemoglobin S gene then the person has sickle cell anemia. The study [6] on SCD by Narcisse Elenga et al. has identified that pregnancy in sickle cell women has numerous obstetrical, non-

obstetrical and fetal complications and requires a support of multidisciplinary team that includes primary physician, Obstetrician and with an integration of Centre for Sickle Cell Disease.

2. HISTORY OF SICKLE CELLS

Gardner [7] in the late 1910, Sickle Cell Disease was discovered and it was abbreviated as "SCD". It was first affected in US but discussion about sickle cell is presented in Africa. Walter clement noel is a dental student studying in Chicago where he was suffering from episodes of pains and symptoms of anemia. He reported to the Dr. James B. Heerick (cardiologist) but the doctor was not interested in the noel's case and he advised Dr. Ernest Iron. Dr. Ernest iron had tested the noel and observed red blood cells are in the "shape of sickle". Noel reported with that reports to Heerick and he got interested because it is an unknown disease. And later he published a journal and termed it as "sickle shaped cells".

A. In Indian Scenario [8]

- First identified in the Nilgiri Hills of northern Tamil Nadu in the year 1952.
- Later it is widespread among the people of Deccan plateau with a smaller focus in Tamilnadu and north of Kerala.

B. In worldwide scenario

- Sickle cells was firstly an unknown disease but now it is spreading over worldwide and it is observed particularly in Spanish speaking regions in the Western Hemisphere (The Caribbean, Central America and South America), Saudi Arabia, India, Mediterranean countries includes(Greece, Italy, turkey) and sub-Saharan Africa.
- Sickle cell deaths are observed more in African-American, with children younger than 4 years of age with sickle cell disease fell by 42% from 1999 through 2002. With the help of vaccination the drop over sickle cell is observed in 2000 which protects against invasive pneumococcal disease.
- During 1990-1994 SCD identified by Newborn screening among mortality children in New York, California and Illinois. By the end of 1995, the mortality rate is 1.5 per 100 in African-American children with SCD in Illinois and California. The mortality rate in African-American or black infants born during this period in

- California and Illinois is 2.0 per 100 Black or African-American or Black.
- SCD is one of the major public health concern where average of 75000 hospitalization due to SCD in US, approximately cost is \$475 million.
 - As per Narcisse Elenga et al. [6] observations, it is found that SCD is serious genetic disorder affecting almost 1/235 births in French Guiana during the observation period between 2007 and 2013.

3. SYMPTOMS AND SIGNS OF SICKLE CELLS [2,9]

- ◆ **Episodes of pain:** It is one of the major symptoms of sickle cell where RBC blocks the blood flow through tiny blood vessels to joints, abdomen and chest. Chronic pain has been observed in adults and adolescents which results in bones, ulcers and joint damage.
- ◆ **Swelling of hands and feet:** Due to sickle cells present in bodies, RBC blocks the blood flow through hands and feet and results swelling in hands and feet.
- ◆ **Frequent infections:** Organ damage (fights infection i.e. spleen), may cause due to sickle cells in bodies. Doctors commonly suggest giving infants and vaccinations and taking antibiotics will prevent life-threatening infections such as pneumonia.
- ◆ **Delayed growth:** If RBCs are getting reduced in human body due to lack of oxygen then the growth can be delayed.
- ◆ **Vision problems:** RBC blocks the blood flow through tiny blood vessels due to sickle cells. These cells do not supply blood to the eyes which may lead to damage of retina. It causes blur vision problems.

4. SICKLE CELLS COMPLICATIONS [9]

- ◆ **Stroke:** Heart strokes may occur if sickle cells block the blood flow in brain system. Symptoms of strokes include weakness or numbness of arms and legs, continuously speaking problem and loss of consciousness.
- ◆ **Acute chest syndrome:** It causes fever, chest pain and difficulty in breathing. It is a very serious complication, which may also lead to life threatening. It requires emergency medical treatment by taking antibiotics and any other treatments.

- ◆ **Pulmonary hypertension:** Patient with SCA report high blood pressure in their lungs (also called pulmonary hypertension). This kind of complication affects adults rather than children. Symptoms of this condition may cause breathing problem and fatigue.
- ◆ **Leg ulcers:** This disease also can cause open sores, in which ulcers may occurs in legs.
- ◆ **Gallstones:** The breakdown of RBC may produce a substance i.e. bilirubin. If bilirubin is having high level in the body which lead to gallstones.

5. TREATMENT FOR SCD

Once this disease is identified in any person, it requires a continuous monitory and treatment. Person with this disease will exhibit the symptoms usually after 5 months of age or during the first year of life. This is due to the infancy stage fetal hemoglobin protects the RBC from sickling formation and when the infant turns to 4 to 5 months, the fetal hemoglobin is replaced with sickle hemoglobin and the cells begin to sickle from then onwards. The exhibits may differ from one person to the other based on the living standards. Over a period of time the person with sickle cells disease becomes worse and need to face sequence of painful episodes. Several types of treatments were available in the present medical environment that can help the people to overcome the problems related to this disease and to improve the lifespan. Treatment like blood transfusions, bone marrow transplantation and medications to reduce the pain are used to prevent the complications in this disease.

A. Blood transfusion:

In this process, RBC was removed from donor blood and then is given to the patient with a process of intravenously. This process could increase the number of normal RBCs in blood flow results to relieve anemia. This process also carry some additional risks like infection and building up of an excess iron in the body that may cause a severe damage to heart, liver and other organs of the body.

B. Bone marrow transplant:

This process involves replacing bone marrow affected by this disease with a healthy donor's bone marrow. Stem cells are the special cells produced by the bone marrow which is a spongy tissue found in the center of some bones. These cells have the capability to turn into different

types of blood cells. This process is initiated only when the bone marrow matches such as a sibling (who does not have this disease). This process requires long stay in hospital and is complicated. The people with this anemia need to take the radiation process (also called chemotherapy) to destroy the existing bone marrow stem cells. Healthy stem cells from the donor blood are injected using intravenously into the patient's bloodstream where they migrate to the bone marrow and start generating new blood cells. These cells start to produce healthy RBCs to replace the sickle cells. Sometimes this process may raise severe complications like the patient's body may reject the transplant process and start attack the other cells in the patient's body which is a life-threatening problem.

C. Medications

The following medications are usually preferred for the patients of SCD:

- ◆ **Antibiotics:** Children with the early detection of SCD start with antibiotic penicillin up to 5 years which mainly prevent from infections such as pneumonia which another life-threatening problem. Adults need to take the penicillin throughout the life.
- ◆ **Pain-relieving medications:** The method of pain relief in the patients is quietly depending on type of pain which is categorized as acute, chronic or a mixture of the both. Doctors' advice and careful observation helps to prescribe the pain medicines [5].
- ◆ **Hydroxyurea (Droxia, Hydrea):** This is a specific medicine preferred for the patients of SCD and is taken daily. This reduces the frequency of painful episodes and might reduce the need of blood transfusions and hospitalizations. Here hydroxyurea stimulates the production of fetal hemoglobin that helps to prevent the formation of sickle cells. The other side of this medicine is it increases the risk of infections and its usage for the long term might cause problems later in life.

D. Other Experimental treatments:

Recent research and Development in the area of Thalassemia and sickle cell disease has also proposed the following treatments:

- ◆ **Gene therapy:** It is an experimental technique which alters the disease causing

gene with a healthy copy of a mutated gene to the body. This process inserts the normal gene into the bone marrow of the people with the disease which will results in normal hemoglobin. The research also exploring the other possibility of turning off the defective gene while reactivating another gene.

- ◆ **Nitric oxide:** The people with this disease have low levels of nitric oxide in their body. This causes and effects on the blood vessels close and increases the stickiness of RBCs. Treatment with inhaled nitric oxide might prevent the sickle cells from clumping together.

6. OTHER KIND OF ANEMIA DISEASE OF SIMILAR KIND

A. Thalassemia [10]

Thalassemia is another abnormal kind of blood disease which is more severe when compared to sickle cell disease as shown in Fig. 3. The major cause of thalassemia is mutation in the DNA of cells carriers from parents to children. Thalassemia is having two kinds of diseases (i.e. Alpha and Beta Thalassemia). The life span of thalassemia cells is approximately 100 days [11]. The symptoms of thalassemia can be observed after 6 months in new born babies because after 6 months normal hemoglobin starts replacing the fetal type. Symptoms are lack of energy, tiredness, breathing problem, pale skin (jaundice), irregular heartbeats.

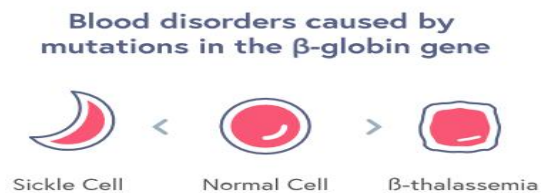


Fig. 3. Difference between normal sickle and thalassemia cells

- ◆ **Alpha thalassemia:** We need 4 alpha-globin protein chains, each individual, two on each chromosome 16. We get two from each parent. If any one of the gene is missing then alpha thalassemia occurs.
- ◆ **Beta thalassemia:** We need 2 globin genes for beta-globin chains, one from each parent. If one or both genes are not matched, beta thalassemia will occur.

Table 1. Gives the comparison study of characteristics of blood cells in normal, sickle cell disease and thalassemia disease people under various parameters

Parameters	Normal cells	Sickle cells	Thalassemia cell
Life span of human beings	More than 70 years [12]	For male 42-45 For female 46-48 [13]	Heart complication may occur before the age of 30 [11,14]
Blood range	For men 14-17.5 gm/dl For women 12.3 to 15.3 gm/dl. [15]	Abnormal Hb level in the range of 6 to 8 gm/dl. [16]	RBC count <13 [17]
viscosity	3-4 centipoise [18]	Increases normal range [19]	Higher than the normal range [20]
RDW(red blood cell distribution width)	11.4-15% [21]	Increased (minor thalassemia) [21]	Normal or slightly decreased [21]
HBA2	2.2 -3.2% [21]	>3.2 [21]	<3.2 [21]
RBC	4.7-6.1 mL (millions cells of microlitre) [21]	Decreased from normal range [21]	Increased from normal range [21]
MCV (mean corpuscular volume)	83-101 (femtolitre) [21]	Decreased [21]	Very Decreased [21]
HbF	<1% [22]	2.1%-10% [22]	1 -3 [22]
HbA	95-98 [22]	50-60 [22]	90-94 [22]
HbS	0 [22]	35-45 [22]	0 [22]
MCHC (mean corpuscular hemoglobin concentration)	31-37 grams per deciliter (g/dL). [23]	Decreased [23]	Slightly decreased [24]
Reticulocytes	0.5 -2.5% for adults [25]	5-15% [23]	>15% [26]
HCT(Hematocrit)	For men 45-57% For female 37-48% [15]	Hemoglobin are above (6-11 g/dl) [27]	Hb levels(9-12 g/dl) [28]

7. TECHNOLOGY USAGE IN THE IDENTIFICATION OF THIS DISEASE

A. Feature Classification and Extraction of Blood Cells Using Artificial Neural Network (ANN) [8]:

- 1) In this paper, quantitative digital- image analysis is used and proposed a novel method to detect the effected blood cells from the normal blood.
- 2) The segmentation of blood cells is used by morphological operations such as dilation and erosion to help to preserve size and shape characteristics. The analysis has extracted features is to get clear idea about normal and abnormal blood cells. Veluchamy et al [8] has used back-propagation algorithm to classify the blood cells for testing purposes. They have also used different size and various types of microscopic blood cell images for the classification and generated the accuracy of 80% and 66.6% for normal and abnormal types respectively.

B. Detection of Sickle Cells using Image Processing [29]:

- 1) In this paper, we found that the presence of sickle cells, ovalocyte and anisopoikilocyte results to severe pain, acute pain and infection. Sometimes this may also lead to brain complications.
- 2) Image processing technology is used for identifying the shape and size of the cells and MATLAB is used for processing different stages like edge detection, segmentation, classification and sickle cell detection.

C. Detection of anemia disease in human RBC using neural networks and SVM and cell signature [30]:

- 1) Anemia is one kind of life threatening disease, in this paper Elsalamony [30] has identified the sickle cell, burr cells, elliptocytosis based on their shape signatures.
- 2) If shapes are in the form of anemia kind of disease, then it is considered as unknown shape.

- 3) In this paper, they use 45 colorful microscopic images for testing of 15 samples by using Circular Hough transforms watershed segmentation and some of the morphological methods to enhance images. The Support Vector Machine (SVM), backpropagation (BP) and self-organizing map (SOM) neural networks used to identify anemia kind of disease with high accuracy.

D. Image processing and diagnosis of sickle cells in Erythrocytes [31]:

- 1) In this paper, Oleiwi et al. [31] identified the count of normal and abnormal RBC cells using the techniques like
 - a) Circular Hough transformation and
 - b) Watershed segmentation.
- 2) Counting of cells is practically important in assessing the level of anemia disease and they have used MATLAB 2015a for this process.

E. Anemia cells detection based on shape signature using NN [32]:

- 1) In this paper, Elsalamony [32] used geometrical shapes signatures method for detection of sickle cells and elliptocytosis in blood samples.
- 2) In the process of detection they have used 30 colorful microscopic images and achieved 100% of accuracy using three neural networks for the anemia kind of disease.

8. PREVENTION METHODS

- 1) **Counseling Process:** This is mostly adopted by the organizations dealing with this kind of anemia patients especially during the time of marriage. If the sickle cell / thalassemia carriers chooses other similar carriers (knowingly / unknowingly), then through counseling process such marriages are discouraged.
- 2) Using hemoglobin electrophoresis test, we can easily diagnose the presence of sickle cell trait especially when there is any kind of family history of SCA and plan to have children.

9. CONCLUSIONS

Sickle Cell Disease is an inherited blood disorder which is originally found in African countries and

spreading to the entire world in rapid manner and need an immediate attention. The awareness, medical developments and research progress about this disease is greatly needed in the present scenario. This paper has presented an in-detailed description about the Sickle Cell Disease (SCD) and its history in international scenario and in national scenario (in the context of India). The symptoms of the disease, signs, complications, treatment and prevention methods for the disease are presented. We have also characterized the blood cells in normal people with that of sickle cell and Thalassemia patients under various blood parameters. This paper also presents the usage of technology for the identification of sickle cell disease with higher accuracy and to develop good prediction models that help to reduce the time and efforts in pain management systems of sickle cell disease.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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