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Technical Report “Sickle Cell Anemia”

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Project "An Environment for Data Analysis of Sickle Cell Anemia"

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ABSTRACT

This technical report aims to present the main characteristics of the Sickle Cell Anemia (SCA), a hereditary and hematological disease, non-contagious, incurable and whose complications are treatable. It also discusses the emergence of the disease and the number of people affected in the United States and Brazil. The main information about SCA is highlighted such as symptoms, treatments and effects. The drug hydroxyurea is cited in the literature as a successful medicine in patients with SCA in order to alleviate the recurrent pain crises. The objective of this report is to provide material for teachers, students, researchers and people interested in the SCA to know the causes and consequences of this disease that affects millions of people and is considered a public health problem in Brazil.

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KEY TO ABBREVIATIONS AND ACRONYMS

SCA	*Sickle Cell Anemia*
SCD	*Sickle Cell Disease*
PNTN	*National Newborn Screening Program*

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1 Introduction

This technical report aims to describe the main concepts related to the "Sickle Cell Anemia". This knowledge is necessary for the members of the project entitled "An Environment for Data Analysis of Sickle Cell Anemia" in order to develop their computational activities, such as the conversion of full scientific papers about this disease from PDF format to XML format, the subsequent information extraction of these papers in XML format, the relational database design to store data about this disease and data mining process. This work is being developed by the University of São Paulo (Campi of Ribeirão Preto and São Carlos city), the Blood Center Foundation of Ribeirão Preto, the Federal University of São Carlos and the Methodist University of Piracicaba.

2 Overview of the Sickle Cell Anemia

Sickle Cell Anemia (SCA) is an inherited (i.e., genetic) and hematological disease (i.e., from blood) that causes chronic destruction of red blood cells, episodes of intense pain, susceptibility to infections and, in some cases, premature death. It affects mainly the African descendants (CONSELHO MUNICIPAL DE DEFESA DOS DIREITOS DO NEGRO, 2008). Genes are inherited from parents, so this sickness is not contagious. Unlike the common anemia that can be cured with food that contains iron, vitamin B12 or vitamin C, the SCA neither has cure, nor can it be alleviated with food. However, it is a treatable disease and the patient can participate in the labor market, once he is receiving adequate medical treatment and has consistent responsibilities with his limitations and potential (SILVA; RAMALHO; CASSORLA, 1993).

The SCA emerged in countries in central-west Africa, India and East Asia, about 50 to 100 thousand years ago, between the Paleolithic and Mesolithic periods (GALIZA NETO; PITOMBEIRA, 2003). Paradoxically, it emerged as a human body self protection from malaria, which is common in regions of warm climate. The disease, which is passed from father to son, spread all over the world as a result of the migration processes, the colonization, and especially, the racial miscegenation (Figure 1). It is more frequent among people whose

ancestors came from Africa, the Mediterranean countries (such as Greece, Turkey and Italy), the Arabian Peninsula, India and regions of Spanish colonization in South America, Central America and parts of the Caribbean (GENETICS HOME REFERENCE, 2007).

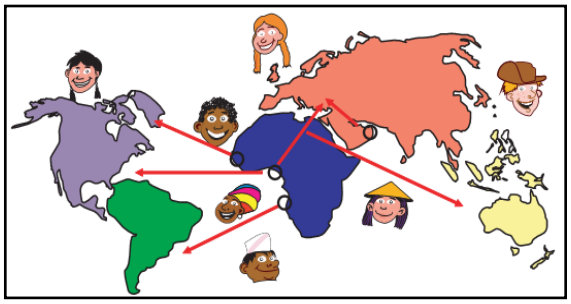

Figure 1 – Racial miscegenation.
Source: Brasil (2007).

Sickle Cell Disease (SCD) affects millions of people worldwide (the difference between SCD and SCA will be explained in Section 3). SCD is the most common hereditary blood disease in the United States, affecting 70,000 to 80,000 North Americans. An estimation of SCD carriers in the United States is 1 in every 500 North American African descendants and 1 in 1,000 – 1,400 North American Hispanic descendants (GENETICS HOME REFERENCE, 2007).

In Brazil, SCA is also the most common inherited disease (ZAGO, 2001) and it is considered a public health problem (SILVA, R.; RAMALHO; CASSORLA, 1993; BATISTA; ANDRADE, 2005; RUIZ, 2007). Besides, SCA was introduced by the slave trade which started in 1550. First, the slaves worked in the industry of sugar cane in the Northeast and later, in the gold mining and precious metal extraction in Minas Gerais (RUIZ, 2007). Not surprisingly, today, Bahia is the state that has the highest focus of the disease in Brazil.

The data of National Newborn Screening Program (Programa Nacional de Triagem Neonatal, PNTN) (apud MINISTÉRIO DA SAÚDE, 2008) show that every year 3,500 children are born with Sickle Cell Disease and 200,000 with sickle cell trait. Generally, twenty percent of these children will not reach the age of five due to complications directly related to the disease. The infant mortality rate in children without any treatment is 25%. Rio de Janeiro Blood Center Data (apud MINISTÉRIO DA SAÚDE, 2008) show a reduction of around 2.4% when the patient receives full attention in the treatment. Therefore, proper treatment has a fundamental role in reducing morbidity and mortality of these patients.

Although SCA is most common in African descendants, any person may have the disease or carry the trait simply due to racial miscegenation. According to PNTN (apud MINISTÉRIO DA SAÚDE, 2008), the highest incidence either of SCA or sickle cell trait is

found in the states of Bahia, Rio de Janeiro and Minas Gerais (Figure 2). In Figure 2, the S gene indicates the incidence of the disease or sickle cell trait.

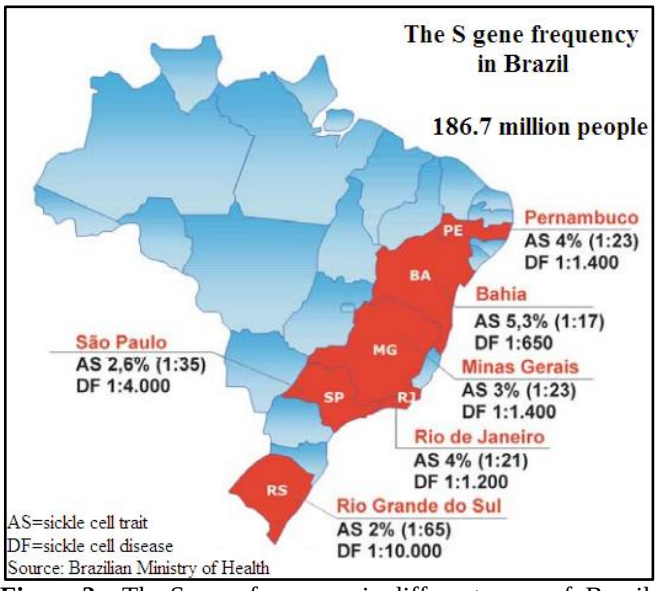

Figure 2 – The S gene frequency in different areas of Brazil.
Source: Adapted from Cançado and Jesus (2007).

3 Characteristics of the SCA

Blood is composed of plasma and three types of cells: platelets (help the coagulation), white blood cells (leukocytes, defense cells) and red blood cells (also known as erythrocytes) (Figure 3). The hemoglobin protein, which is rich in iron, is inside the red blood cells. The hemoglobin protein is responsible for the red color of blood and for carrying oxygen throughout the body, making the body's vital functions work perfectly.

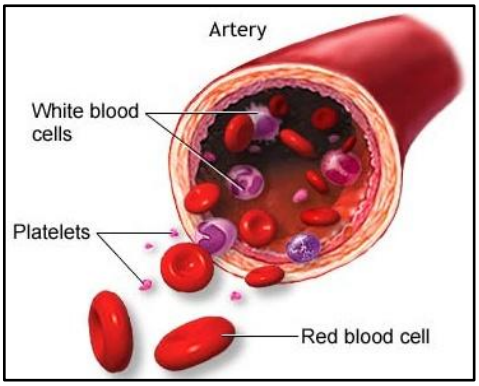

Figure 3 – Blood elements.
Source: Medical Encyclopedia (2008).

What differentiates SCA from common anemia is that, in the first one, hemoglobin A (common) is replaced by hemoglobin S, which has the sickle shape, hence the name sickle cell (Figure 4). In people with common anemia "only" a reduction of hemoglobin in the blood

occurs (it is estimated that 90% of the cases are due to lack of iron, known as iron deficiency anemia (MINISTÉRIO DA SAÚDE, 2004)).

Figure 4 – Red blood cells in sickle shape (half moon).
Source: Rodrigues (2008).

Sickled red blood cells pass in the blood vessels with difficulty (i.e., veins and arteries). They cause intense pain crises that often occur in the abdomen, lungs, bones and body joints in the patients. The sickled red blood cells are rigid and sticky and tend to form projections and become trapped in the blood vessels. Figure 5 shows the flow of a normal red blood cell **(a)** and the problem that sickled red blood cells cause in the blood circulation **(b)**.

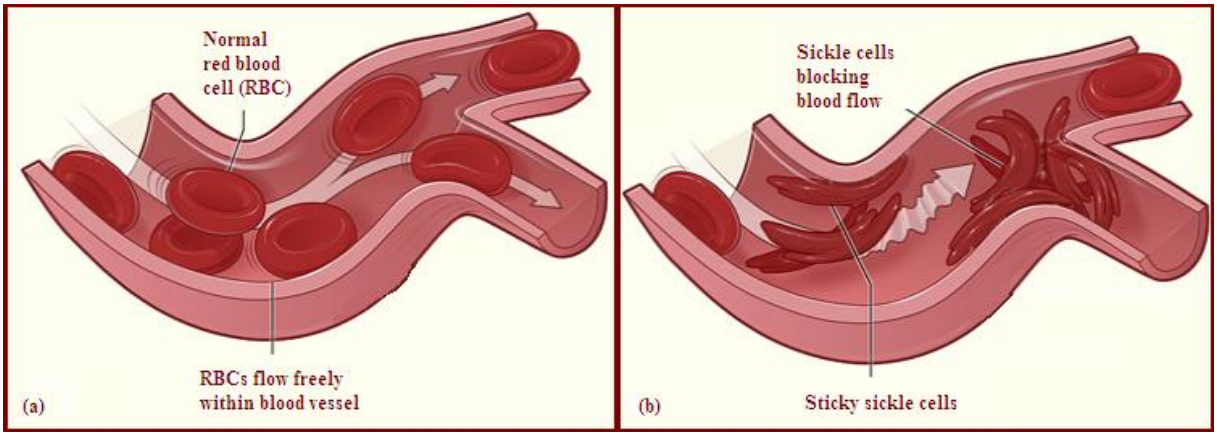

Figure 5 – Red blood cell (a) and Sickled red blood cell (b).
Source: Adapted from National Institute of Health (2008).

The red blood cells are produced in the bone marrow which is found in large bones of the body. In average, they last 120 days in the bloodstream and then die. In SCA, the low number of red blood cells occurs because the sickled red blood cells do not last much time (in average of 10 to 20 days) (NATIONAL INSTITUTE OF HEALTH, 2008). The bone marrow is responsible for producing new cells constantly to replace the old ones. However, regarding an individual who has SCA, the bone marrow is unable to produce new cells rapidly to replace those that are dying, which causes intense pain crisis, harmful oxygen spreading to the cells and other problems arising from lack of healthy red blood cells.

A person without the disease gene inherits hemoglobin A (homozygous AA) from the father and the mother. For a person to be born with the SCA gene it is necessary to inherit hemoglobin S from both the father and the mother (homozygous SS). Who inherits hemoglobin A from one of the parents and hemoglobin S from the other one has a condition

called sickle cell trait (heterozygous AS). People who have sickle cell trait are not sick and have no symptoms either (asymptomatic), but they may have children with SCA. Figure 6 depicts the probability of a sickle cell trait couple to have children with SCA (25%, SS genes), the same probability of having children without the disease (25%, AA genes) and 50% probability of having sickle cell trait children (genes AS).

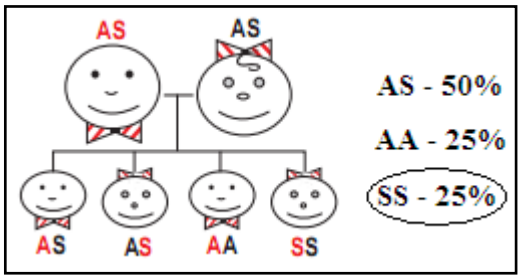

Figure 6 – The probability to be born with Sickle Cell Anemia, considering that parents are heterozygous AS. *Source*: Adapted from Hemorio (2005).

The person with SCA has the SS gene, which is peculiar to the disease. However, there are several varieties known as Sickle Cell Disease (hereditary abnormalities of hemoglobines), for instance, individual S with another abnormal hemoglobin (e.g., C, D, Thalassemia), causing hemoglobin like SC, SD, S-Thalassemia (MINISTÉRIO DA SAÚDE, 2008).

4 Information of Interest in the Study of SCA

In the field of Sickle Cell Anemia, information is divided into seven categories: patient, symptoms, treatment, risk factor, disease effect, side effect of the treatment and positive effect of the treatment. Each of these categories is explained below:

- **Patient:** Information related to the number of patients: total of patients rolled-up, all patients who have successfully completed the treatment, all patients who have not had a good result with the treatment (e.i, some complications or even death), total of patients who have suffered from the disease, all patients who have suffered from side effects of the treatment, all patients who have had positive effects with the treatment, all patients who have undergone each treatment and total patients who have presented some symptoms;
- **Symptom:** The characteristics that allow the identification of the disease which are reported by the patient or identified by clinical examination. Examples: pain, cough, fever and dyspnea (i.e., shortness of breath or breathing difficulty);

- **Treatment:** Use of a drug or application of a therapy for a period that allows modification in the patient's health regarding the disease. Examples of drugs: hydroxyurea and folic acid. Examples of therapy: bone marrow transplantation and blood transfusion;
- **Risk Factor:** Any characteristic that can worsen the patient's health. This characteristic does not allow the SCA identification (i.e., symptoms), nor is it due to the disease (i.e., effects). Examples: exposure to cold, sudden temperature changes, menstruation, pregnancy, stress in adults and dehydration;
- **Disease Effect:** Any negative effect (or complication) intrinsic to the disease resulting from sickle red blood cells independent of the use of a particular treatment. Examples: acute chest syndrome, splenic sequestration and cardiac ischemia;
- **Side Effect of the Treatment:** Problems caused by the treatment stimuli, that is, the negative effect of a treatment (i.e., drug or therapy). Examples: lymphoma, leukemia and depression;
- **Positive Effect of the Treatment:** Improvements or benefits caused by the treatment stimuli, that is, the positive effect of a treatment (i.e., drug or therapy). Examples: healing, remission and reduction of the hospitalization time.

4.1 Complication and Symptom

Some symptoms of Sickle Cell Anemia (SCA) are similar to the common anemia, including fatigue, weakness, pallor (especially on the conjunctiva and palms), jaundice (icterus), poor concentration and vertigo (i.e., dizziness). Moreover, other symptoms intrinsic to SCA, for instance, pain in the body joints and dyspnea, are caused by the accumulation of sickle red blood cells in blood vessels and by the increase of the blood viscosity. Because of this, there may be clots in different parts of the body, with a deficit in transporting blood into the affected body region.

SCA can cause several complications depending on the patient's age such as a sequestration crisis (a sudden and abrupt retention of large volumes of blood in the spleen), leg ulcers (sores around the ankle and on the side of the leg), priapism (painful penis

erection), cerebrovascular accident (CVA) or stroke (interruption of the blood flow in the brain by cerebral infarction), among others (BRASIL, 2009).

In infants, infection and pain with swelling are concentrated in hands and feet. In older children, the pain is generally located in the legs, arms and belly (BRASIL, 2007). In adults, pains occur mostly in the bones, liver, lungs, heart and kidneys. SCA patients face several kinds of infections such as autoesplenectomia and salmonella since childhood (DI NUZZO; FONSECA, 2004). According to Gómez-Chiari, Puigbert and Aramburu (2003 apud DI NUZZO; FONSECA, 2004), infections are the most common complication in individuals with SCA.

4.2 Prophylaxis

There is no cure for SCA because it is a hereditary disease and its manifestations can vary according to each individual’s body. Thus, prophylaxis of the SCA complication is indispensable to provide quality of life to these individuals. Therefore, it is necessary (DI NUZZO; FONSECA, 2004):

- Neonatal diagnosis followed by guidance and family education program through outpatient referral process;
- Prophylaxis with penicillin;
- Vaccination at appropriate ages against encapsulated organisms such as *Haemophilus influenzae type b* (Hib) and pneumococcus;
- Early identification of febrile episodes considered as potential septic events.

Early diagnosis of SCA is able to monitor the child before symptomatology and complications show up, and it makes it possible to start antibiotic prophylaxis since 3 months old, together with vaccination against encapsulated bacteria. This reduces the number of deaths associated with the disease significantly and it provides a better quality of life. Death is mainly caused by infection problems (reduction from 30% to 1%) (GÓMEZ-CHIARI; PUIGBERT; ARAMBURU, 2003 apud DI NUZZO; FONSECA, 2004). Countries that have established the neonatal examination for these hemoglobinopathies have shown that the children monitored in specialized centers can have mortality from pneumococcal infections reduced from 40% to 10% and overall mortality reduced from 8% to 1.8% (SILLA, 1999 apud DI NUZZO; FONSECA, 2004).

4.3 Diagnosis

The diagnosis can be performed when the child is born by a procedure known as newborn screening, Figure 7 **(a)**. It is also possible to diagnose the Sickle Cell Anemia with the screening tests known as sickling test and smear test. To confirm the result of the screening test the Hemoglobin electrophoresis is performed, Figure 7 **(b)**.

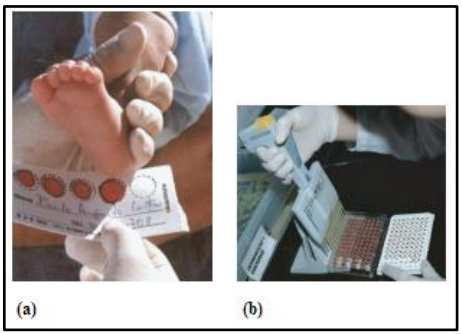

Figure 7 – Newborn screening (a) and Hemoglobin electrophoresis (b).
Source: Adapted from Brasil (2007).

4.4 Drug Hydroxyurea

Several studies go towards alleviating the suffering of patients with SCA. The drug hydroxyurea has been used in patients who have recurrent painful crisis or acute chest syndrome. This drug has been used since 1995 when the first results were obtained in adults (CHARACHE et al., 1995). Real benefits are found at different age groups, but the effectiveness of the treatment with this drug in the long term, especially in children, is still uncertain (GULBIS et al., 2005).

In addition, hydroxyurea is considered the most successful drug against SCA (GULBIS et al., 2005). It can increase the concentration of fetal hemoglobin which can reduce the severity of the disease, producing improvement in the clinical status. By using this drug, patients may additionally have the following benefits (BRASIL, 2002):

- Growth in hemoglobin F production and mild increase in the total concentration of hemoglobin;
- Reduction of acute chest syndrome episodes, the number of hospitalizations and the number of blood transfusions.

5 Final Considerations

Several medical papers about Sickle Cell Anemia have reported success with the drug hydroxyurea (CHARACHE et al., 1995; COVAS et al., 2004; LEFÈVRE et al., 2008) and with therapy such as blood transfusion (STYLES et al., 2007; BADER-MEUNIER et al., 2009). These papers have been published in several journals (e.g., American Journal of Hematology,

Blood, British Journal of Hematology, Haematologica, The New England Journal of Medicine, among others).

One motivation for automating the processing of scientific papers comes from the fact that there is a lot of information which researchers are unable to process due to the myriad of conferences. This huge quantity of information requires an exhaustive search to find an interesting paper (which takes time), and longer still, to read them and to extract the main information, for example, information about patients, symptoms, risk factors, treatments, disease effects, side effects of the treatment or positive effects of the treatment.

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