



A Review on Journey of Sickle Cell Anemia: Breakthrough and Occurrence with Special Reference to India

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Abstract

Sickle cell disease is a genetic disorder in which RBCs of patient becomes sickle shaped, thereby decreasing oxygen carrying capacity. It is not necessarily expressed since birth but may appear in any age. It is caused by a gene that is heterozygous, it results in abnormal haemoglobin known as HbS. The polymerization of HbS alters both the structure and function of erythrocytes, initiating a cascade of events that ultimately affect a wide range of tissues. In India, the disease is found in many people who are unaware of it and usually remain untreated. Indian government is also running few programs to make people aware and proceed for treatment. The disease was first discovered in 1910, since then a sequence of studies has been done, and still going on to fight against the disease. The frequency of disease is more in people of tribal area in India, who belong to specific caste.

Key words: Sickle cell disease; RBCs; erythrocytes; HbS; polymerization.

Introduction

Sickle cell disease (SCD) was first described in 1910, in a student of dental college who presented pulmonary symptoms [1]. Herrick has given the term “sickle-shaped” to describe the specific appearance of the RBCs of the dental student. However, considering patient’s symptoms, he was not sure at that time whether the blood condition was a special case of a disease or a manifestation of another disease [2]. In the next 15 years, several similar cases were reported, supporting the idea that this was a new disease entity and providing enough evidence for a preliminary clinical and pathological description [3]. Shortly thereafter, Hahn and Gillespie suggested that anoxia caused RBCs sickling by demonstrating that shape changes could be induced by saturating a cell suspension with carbon dioxide [4]. Scriver and Waugh, proved this concept, in their experiments performed in vivo by inducing venous stasis in a finger using a rubber band. They showed that stasis-induced hypoxia dramatically increased the proportion of sickle-shaped cells from approximately 15% to more than 95% [5]. These seminal studies were noted by Linus Pauling, who was the first to hypothesize (1945) that the disease might originate from an abnormality in the hemoglobin molecule [6]. This hypothesis was validated by Pauling et al in 1949 by the demonstration of the differential migration of sickle versus normal hemoglobin as assessed by gel electrophoresis [7]. That same year, the autosomal recessive inheritance of the disease was elucidated [8].

Around the same time, Watson et al. predicted the importance of fetal hemoglobin (Hb F) by suggesting that its presence could explain the longer period necessary for sickling of newborn RBCs compared with those from mothers who had “sickleemia” [9]. Ingram and colleagues demonstrated shortly thereafter that the mutant sickle hemoglobin (Hb S) that caused SCD differed from normal hemoglobin A, by a single amino acid [10]. This was followed by studies that analyzed the structure and physical properties of Hb S, which formed intracellular polymers upon deoxygenation [11]. These studies placed SCD at the leading edge of investigations to elucidate the molecular basis of human diseases.

In 1911 shortly after Herrick's discovery, a 25 years old female patient was known to describe symptoms of sickle cell disease. She was under the treatment for several years but previously diagnosed as pernicious anemia with atypical characteristics. In 1915 the third recorded case of SCD was a 21-year-old female that showed the slide prepared from her blood sample was similar to indicate this disease. The blood film of her father was also examined, which made this case much clear. It was noted that in the fresh blood sample there were no abnormalities but some abnormal cells appeared after a few days. This became the first crude test of SCD and was the first time that the disease was suggested as an inherited condition. The fourth case of SCD was a 1922 a 21-year-old male patient who was in published literature and the first case that was used the term “sickle cell anemia.” [12,13, 14]

Verne Mason [15] noted a common thing among the first four cases of disease that were recorded, which included the fact that all patients belong to the African region. This led to a common assumption over the following few years that the disease was limited to only this population group; since then, this association has not been found to be true. In fact, many other populations are affected by SCD, which belong to the Arabian Gulf, Central India, the Mediterranean area of northern Greece and southern Italy, as well as eastern Turkey.

SCA, therefore, [45] has always been at the top priority of molecular medicine and arguably launched the complete field of human molecular genetics. Because of the genetic simplicity of the disease, being caused by a change in single gene, it has been used to illustrate and validate many of the advances in this field, including proof-of-principle studies in DNA diagnostics, predictive genetics, and population and epidemiological genetics [46, 47, 48, 49]. The contribution of genetic modifiers to its extreme clinical heterogeneity made SCA an exemplar of the effects of genetic background on a single-gene disease. More recently, SCA has demonstrated the potential for genome-wide association studies in the discovery of interacting genes that might be of clinical or therapeutic significance. Genome wide association studies of HbF (foetal haemoglobin), a quantitative trait that influences SCA severity, identified two quantitative trait loci that are not linked to the HBB cluster: BCL11A and HBS1-MYB [50, 51]. These results have led to various genetic approaches to the reactivation of HbF that are now being explored as therapeutic options in SCA [50].

Clinical variability of SCA contribute to the both environmental and genetic factors. Although the importance of climate as a trigger of acute pain has been suggested for many years, but it is very difficult to prove for logistic reasons [52]. There are studies on twins, suggesting that environmental factors in general are important determinants of the clinical course of SCA. This study include two case reports limited to single pairs, one with HbSS and α -thalassemia and the other with HbS and β -thalassemia [53, 54], and from Jamaica total nine pairs of identical twins were studied; six with HbSS and three with HbSC [55]. These studies show that, there is considerable discordance in the frequency of painful crises and other complications even if twins may have similar laboratory parameters and are of similar heights and weights. Furthermore, other environmental factors influence risk factors such as infections, including nutritional status and exposed to medical care and social support [52]. Factors that influence the primary event of HbS polymerization (including coexisting α -thalassemia and HbF concentrations) have a global effect on the phenotype of the disease. Approximately one-third of SCA patients of African descent also have α -thalassemia, usually caused by the common African 3.7-kb ($-\alpha 3.7$) deletional variant [56]. While the majority are heterozygous ($\alpha\alpha/-\alpha 3.7$), 3–5% are homozygous ($-\alpha 3.7/-\alpha 3.7$). Due to coexisting α -thalassemia HbS is reduced intracellularly which results in decrease in mean corpuscular hemoglobin concentrations, reductions in the frequency of HbS polymerization and number of sickled cells irreversibly, and an increased hematocrit [57, 58]. While some of these effects are beneficial, others are harmful. SCA Patients with α -thalassemia have a reduced risk of hemolytic complications, such as pulmonary hypertension, cardiomyopathy, nephropathy, priapism, and leg ulcers, but an increased risk of vaso-occlusive

complications, such as ACS (Acute coronary syndrome), painful crises, osteonecrosis, and retinopathy [59]. There are several studies demonstrating an association with lower TCD (transcranial doppler) velocities and stroke [60, 61, 62]. The bilirubin is reduced due to reduced hemolysis, with a quantitative effect that is independent of that of the UGT1A1(UDP glucuronosyltransferase 1 polypeptide 1) promoter polymorphism [56]. However, coinheritance of α -thalassemia obstructs the response to hydroxyurea therapy, potentially because the HbF and mean corpuscular volume responses are affected [63].

For the first time in 1949 [7], it was shown by electrophoresis that the rate of movement of sickle hemoglobin was different as compared to normal hemoglobin, suggesting a molecular change in the abnormal cell. Opportunities to differentiate among different forms of SCD became possible when hemoglobin electrophoresis became widely available in 1954. This led to different forms of haemoglobin and sub-classification of the disease, as we know them today.

A summarized discovery regarding Sickle cell anemia

1910	James Herrick has given the term sickle-shaped to the peculiar, elongated RBCs in a dental student who was patient of anemia [1]
1933	Lemuel Whitley Diggs suggested that pain occurs in patients with sickle cell is due to clogging up of sickle cells to small blood vessels [16]
1949	Linus Pauling proposed that the abnormal hemoglobin causes sickle cell disease [7].
1957	Vernon Ingram discovered that sickling of cells is due to change in one amino acid in hemoglobin S (HbS). He [10,18] also explained that a single amino acid substitution i.e. glutamic acid changed to valine at 6 th position of β -globin chain in hemoglobin.
1963	Goldstein et al. [17] showed that the substitution of single amino acid occurs from the change in single base (A to T) at codon 6 (rs334).
1971	Whitten and Dorothy Boswell established, the Sickle Cell Disease Association of America. They also formed the Sickle Cell Detection and Information Center.
1972	The Indian Government gives funds for screening, research, and treatment of SCD under the Sickle Cell Anemia Control Act. As a result of this fund National Heart, Lung, and Blood Institute establishes the Cooperative Study of Sickle Cell Disease [69].
1980	Robert P. Hebbel discovered that sickle cells stick to the lining of blood vessels and showed the correlation of sticking of cells with severity of illness in the disease [20].
1983	The Prophylactic Penicillin Study (PROPS) by Cober and Phelps suggested that sickle cell patients can be treated with penicillin which could prevent death of serious infections [21]
1995	The Multicenter Study of Hydroxyurea has proved that the hydroxyurea is useful in preventing complications in sickle cell disease patients [22].
1996	Walters and Patience studied The Multicenter Bone Marrow Transplant and demonstrated a cure for children with the disease (SCD) [23].
1998	Clinical trials showed, an effective screening tool for SCD so that the Stroke Prevention in Sickle Cell Disease can be done by transcranial Doppler ultrasonography which is a method of blood flow analysis in the brain [69].

2000	Lenette J. Benjamin demonstrated that the treatment of pain in hospitals improves quality of life and prevents hospitalizations. Free haemoglobin results due to Hemolysis (a breakdown of red blood cells), which decreases the availability of an important signaling molecule called nitric oxide, causing many pathologic consequences, including pulmonary hypertension. He further suggested a common symptom, that is, pulmonary hypertension is in sickle cell disease which causes death of patients [24].
2001	A mouse suffered from sickle-cell anemia was successfully recovered with the help of Gene therapy [25].
2005	Analysis of 108 SNPs in 39 candidate genes in 1,398 individuals with SCA was done to predict complications of sickle cell disease, Genetic methods were developed. Using Bayesian networks, it was found that 31 SNPs in 12 genes interact with fetal hemoglobin to modulate the risk of stroke [70].
2007	Techniques were developed to convert normal cells into stem cells in sickle-cell mice which was used for gene therapy and transplant as treatment of SCD [26].
2008	Biologic parameters were obtained at baseline. alpha-thalassemia was present in 155 of 325 and G6PD deficiency in 36 of 325 evaluated patients. TCD was abnormal in 62 of 373 patients [60].
2008	Although Hydroxycarbamide (HC) is a key drug therapy in sickle cell disease (SCD), does not show a clinical response in every patient. Among all SCD patients, approximately 30% have co-inherited alpha-thalassaemia resulting in hypochromic and microcytic erythrocytes. [63].
2009	A major complication in SCD patient is the avascular necrosis of femoral and humoral heads. The frequency of this symptom is highest in HbSS and α -thalassemia [50].
2010	Contrary to the common earlier belief, it is also seen in non ribal population in central India, Orissa and Andhra Pradesh. The incidence of β^S gene varies from 0 to 40 per cent and the relatively high frequency of β -thalassaemia in the same population groups often leads to the clinically important condition, sickle haemoglobin β thalassaemia. In S- β -thalassaemia, the clinical manifestations were mild in majority of patients unlike β -thalassaemia major [64].
2011	Prenatal diagnosis for SCD may not be absolutely indicated since the severity of disease is less but neonatal screening is absolutely essential to improve the QOL (quality of life). It is possible even in the remote areas in tribal communities to do neonatal screening but the success depends upon the careful genetic counselling [66]
2013	Common morbid events during infancy include hand-foot syndrome, febrile illness, acute painful events and acute febrile illness being most common. SCD children are more prone to infection. <i>Staphylococcus aureus</i> and Gram-negative bacteria accounted for all cases of bacteraemia [65].
2017	Recently, a systematic screening to prevent stroke risk is available. It includes non-invasive MRI and other diagnostic apparatus, but the role of haemolysis, management of pregnancy in women, and cerebrovascular disease is yet not clear and controversial [33].
2018	Hockham C. generated the first model-based map of frequency of sickle-cell allele specially in India which reveals the proper distribution of scheduled and non-scheduled populations at district level. Where possible number newborns could be derived in the two groups of SCA, at state- and district-level [67].
2022	The study highlighted the spectrum of haemoglobinopathies seen in a population with study subjects hailing from different geographical areas across India. Thalassemia minor and HbS trait are the most common haemoglobinopathies detected [68]

Sickle cell disease in India

Sickle Cell Disease (SCD) which is a genetic condition, is widely present among the tribal population in India where about 1 in 86 births among STs have SCD. It directly affects haemoglobin (responsible for carrying oxygen in the body) in RBCs. The morbidity and mortality are caused by haemolysis of Hb. Therefore, an early detection and treatment of SCD is most important for improvement of health conditions [27].

In tribal areas, The Ministry of Tribal Affairs (MoTA) has launched the Sickle Cell Disease Support Corner to link the patients and health care services. The Portal started by the government provides a registration system on web which collects and saves all information related to SCD among tribal people and other affected people in India, and provide them a platform for treatment if they have the disease.

The portal gives access to real time data through a dashboard, online self-registration facility, and convey information about the disease and various efforts of government. A council for the disease is also formed, known as National Council on Sickle Cell Disease that is constituted of senior officials and some private bodies that are directly involved in these activities [28].

Today, with a high prevalence in sub-Saharan Africa, parts of Mediterranean, India and in the Middle East, SCD is the most common and severe monogenic disorder in the world, [30]. The highest prevalence of the disease is in India in South Asia, where over 20 million patients with SCD are found. Various approaches, including village-level prevalence surveys as well as State-wide screening programmes, prevalence of SCD in India has been quantified [31], the main focus is on groups with the β^S allele prevalence. Screening is generally dependent upon solubility test of Hb at the point of care, but this test does not distinguish sickle cell trait (HbAS) from SCD and therefore requires further testing [29]. The screening of new born under the Pilot projects for SCD in the various states including Gujarat, Maharashtra and Chhattisgarh resulted in obtaining the numbers of HbAS prevalence ranging from two to 40 per cent [29]. The central India showed the highest frequency (up to 10%) of the β^S allele, from South-Eastern Gujarat to South-Western Odisha [30]. India has been ranked the country with the second highest numbers of predicted SCD births, with 42,016 [interquartile range (IQR): 35,347-50,919] newborns estimated to have been born with sickle cell anaemia in 2010 [30,32].

Being a neglected health problem, the overall research on sickle cell disease (SCD) is not sufficient in India [33,34,35]. It is evident that the research on SCD is very fragmented because of different disciplinary areas, such as biomedical disciplines (especially haematology, pathology and genetics). The WHO provides an environment of health system and includes all organizations, whether they are government or non-government, people those belong to social groups and active members whose main motive is to promote, maintain health and make the maximum, use of available resources [36,37]. A draft policy notified by the Ministry of Health and Family Welfare exists, although, there are currently a few national or state-level programmes for SCD, [38]. However, remote tribal populations, there are few non-governmental organisations (NGO) that are actively participating to resolve the problem with limited resources and public health services.

Since the early 20th century, various haemoglobinopathies have been described. The sickle-cell haemoglobin is the result of an amino acid substitution due to a point mutation in the gene coding for one of the constituent proteins of haemoglobin. It was first of all examined in India by Australian and British pathologists. In 1950s and 1960s a survey was done among various communities in India, in which the SCD prevalence was observed specially among tribal populations that shows high variation within and across tribal communities [39], ranging from as low as 1% to as high as 40%–55% [40]. Since then, the prevalence of SCD is usually described as higher among particular tribal communities but socially disadvantaged population groups those do not belong to tribal such as other backward classes and scheduled castes [40]. Recent reviews of SCD are comprehensive [41] and have summarized its occurrence in specific area and prevalence of population with the help of surveys. However, it is evident that the socially neglected population groups face difficulties to get good and frequent health services and so it becomes necessary to create an ideal health system for the affected people to identify gaps regarding the disease and its treatment. With the help of people who are associated with research, and human agencies, a better health system can be developed. [42]. Hence, Raman et al suggested to examine thoroughly the research available from a health policy and systems research lens advancement to make a better approach towards action on SCD [43].

A study of Rajiv et al majority of the patients belong to scheduled caste communities (47.9%) and Gond tribal community (13.8%). The most common clinical manifestation observed was Splenomegaly (71.4%). Overall, 63.5% patients had a history of blood transfusion. Generally Pallor, Icterus, Joint pain, Fever, and Fatigue are the most common signs and symptoms were observed. Onset of disease prior to attaining the age of 3 years was observed in most of the patients (sickle cell anaemia 44.3% and sickle beta thalassaemia 35.9%). Mean haemoglobin levels were marginally higher among SCA individuals than SBT (spontaneous breathing trials) patients. On the other hand, mean foetal haemoglobin levels among SBT individuals showed a lower mean haemoglobin levels [44].

Conclusion

Sickle cell anemia is a big problem in the world. Its treatment is not yet under the reach of common people. In India people should be aware of the disease and its consequences. Common people, NGOs, social groups and government all must fight together against it because being a genetic disorder its treatment is too costly and uncommon for common people. Even the tribal populations are not aware of the disease in which the disease is most common.

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