Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Special Article - Anaemia

How Do Sickle Cell Genes Protect Tribal People from Deadly Malaria? Is This a Type of Natural Selection?

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Received: July 28, 2023

Accepted: August 30, 2023

Published: September 14, 2023

Abstract

In humans, genetic mutations have led to the formation of several haemoglobin (Hb) variants during human evolution. These mutations usually occur in the genes for α and β- polypeptide or globin chains of haemoglobin located on chromosomes 11 and 16, respectively. Among these haemoglobin variants, sickle cell haemoglobin (Hb-S) is highly significant in the humans. In fact, this abnormal or mutant haemoglobin is the resultant of a point mutation in the gene for β-globin, located on chromosome 11. No doubt, this sickle cell gene is relatively more prevalent among tribal people and widely distributed in those geographic regions where the dreaded *Plasmodium falciparum-malaria* is hyperendemic. In the human population, this mutant gene exists in two forms, the heterozygous (Hb-AS) and homozygous (Hb-SS) states. But this sickle cell gene is also found in association with other mutant genes of erythrocyte or red cell genetic disorders, such as abnormal Hb-C, β-thalassemia, G-6-PD enzyme deficiency, etc.

It is well known that tribal people generally live in forest ecosystem where dreaded malaria is also found to be endemic. How have these tribal people been able to protect themselves from this dreaded malaria for thousands of years in such a hostile environment, when they were most likely to be infected with the malaria parasite? Actually, its secret is hidden in these sickle cell genes only. Tribal individuals who have these genes in the heterozygous state (Hb-AS) do not get malaria or are protected from malaria and lead a healthy life. Several studies have confirmed that AS heterozygote people are protected against malaria. In contrast, those who have these genes in the homozygous (Hb-SS) state (homozygotes) develop sickle cell anaemia, which is fatal. Such patients die early due to severe malaria i.e AS heterozygotee individuals have a double advantages. In fact, it is a type of natural selection and also shows a balanced polymorphism in tribal people which is based on Darwin's theory. This current communication provides factual and scientific information about the origin of sickle cell genes in the context of natural selection and how these genes protect tribal individuals from malaria. This communication is useful and important for zoologists, scientists working on human evolution, and medical scientists.

Keywords: Alleles; Erythrocytes; Haemoglobin; Homozygotes; Heterozygotes; Malaria; Natural selection; Sickle cell gene; Sickle cell haemoglobin; Sickle cell anaemia; Sickle cell trait; Tribals

Citation: Choubisa SL. How Do Sickle Cell Genes Protect Tribal People from Deadly Malaria? Is This a Type of Natural Selection?. Ann Hematol Onco. 2023; 10(5): 1437.

Introduction

Except perhaps Africa, India has the largest population of tribal people in the world. In a way, these people are also called the children of nature and their lifestyle is determined and molded by the ecosystem. There are over 533 tribes in India that live in diverse forest ecosystems. As per 2011 census, 10.42 Cr. Indians notified as 'Scheduled Tribes' (ST) constitute 8.6% of the total population in the country. In 2001, the tribal population of India increased to 10.43 million from 8.43 Cr. In the world, among diverse ethnic groups or tribes, many tribes are still primitive types that still survive in hostile environments where malaria is more prevalent and highly endemic. It is well known that malaria is fatal, which is caused by infection with *Plasmodium falciparum*-malaria parasite. According to the recent World Malaria Report, 2022, by World Health Organization [1], thousands of people die due to malaria worldwide every year in malaria endemic countries. Interestingly, the malaria parasite and its vectors and the tribal people have been living together for thousands of years or centuries and are still living together, yet the tribal people are still alive and protected from malaria infection. After all, how do these tribal people escape from malaria and stay safe? In fact in these tribal people it has been possible by natural selection. Probably this is a wonderful, unique and rare example in human biological development or evolution.

In fact, malaria itself is an important biological factor responsible for this natural selection [2,3]. During biological evolution, this malarial strain or pressure caused a mutation in the β-polypeptide or globin gene on chromosome 11 associated with human red blood cells (erythrocytes), leading to the formation of sickle cell haemoglobin (Hb-S) in these cells [4]. Because of this, the shape of the blood cells becomes sickle (Figure 1). These mutated β- globin genes are also known as sickle genes, which inherited from one generation of tribals to another, which are still present in them. These sickle genes are responsible and capable of protecting these tribals from deadly malaria [5-21]. In addition to the sickle cell gene, some other genes for red cell genetic disorders, such as Hb-C, β-thalassaemia, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, and blood groups are also found for genetic resistance to malaria in human populations [22-36]. This current communication provides factual and scientific information about the origin of sickle cell genes in the context of natural selection and how these genes protect tribal individuals from malaria. This communication is useful and important to zoologists, scientists working on human evolution, and medical scientists.

Sickle Cell Haemoglobin (Hb-S)

Human or mammalian haemoglobin (Hb) is a tetrameric conjugated protein composed of two subunits, each of the α (alpha) and β (beta)- polypeptide or globin chains. Each polypeptide chain is attached to a heme prosthetic group. These chains are made up of amino acid residues. The α-chain consists of 141 residues while the β-chain consists of 146. Thus normal adult Hb (Hb-A) consists of two α and two β-chains and is composed of 574 amino acid residues [37,38]. Globin chains are produced in the cytosol of erythrocytes and occur by genetic transcription and translation. The presence of heme in the erythrocyte induces globin gene transcription. The alpha and beta- chain genes are located on chromosomes 16 and 11, respectively. The heme prosthetic group is synthesized both in the cytosol and mitochondria of erythrocytes [37,38].

The synthesis of sickle cell haemoglobin (Hb-S) is the result of a single base-pair point mutation (GAG to GTG) in the β-polypeptide or globin gene located on chromosome 11. This genetic mutation is responsible for the substitution of the amino acid glutamic acid (hydrophilic) for valine (hydrophobic) at the 6th position of the β-chain of haemoglobin (β6Glu) → Val), the resulting Hb is called sickle cell haemoglobin (Hb-S). In fact, this amino acid substitution leads to the formation of linear polymers of deoxygenated Hb-S. The gene responsible for Hb-S synthesis is known as the sickle cell gene. Heterozygous individuals (heterozygotes) have a mutation in only one of the two β-globin chains, resulting in sickle cell trait (Hb-AS). Resistance to *falciparum*-malaria infection and complications are benefits of the sickle cell trait. Homozygotes have mutations in both β-globin chains, resulting in sickle cell disease. When deoxygenated, Hb-S causes deformation of erythrocytes from a bulging disc into a crescent or "sickle" shape. This change in shape damages erythrocyte membranes, causing premature destruction of erythrocytes and chronic hemolytic anaemia. Sickled erythrocytes can obstruct blood flow and cause tissue hypoxia, which can lead to severe ischemic pain or even stroke. These patients also have functional asplenia and are at risk of infection with encapsulated organisms [39,40]. This abnormal Hemoglobin (Hb-S) was discovered by Herrick in 1910 in a black student in the West Indies [4]. His blood film revealed the presence of sickle shaped RBCs or sickle cells (Figure 1).

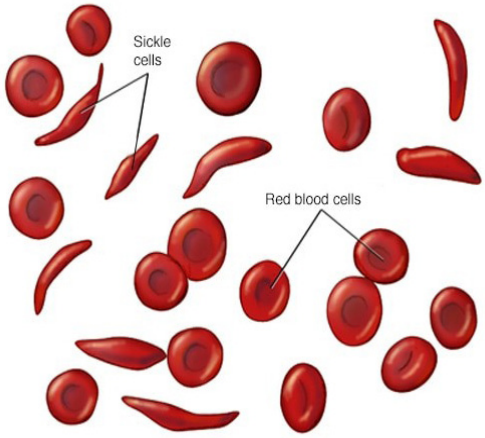

Figure 1: Red blood cells or erythrocytes are usually round and flexible. But in sickle cell anaemia, some red blood cells appear in sickle forms.

Sickle Cell Genes among Tribal People

The prevalence of sickle cell trait varies markedly between different regions, but reaches as high as 40% in some regions of sub-Saharan Africa, eastern Saudi Arabia, and central India, where fatal malaria is also endemic [40,41]. In the Scheduled Tribe (ST) population of India, the prevalence of sickle cell gene ranges from 0 to 35% in different ethnic groups of the tribes. Tribal groups with high prevalence of Hb-S (20–35%) include Bhils, Madiyas, Pawaras, Pardhans, and Otkars [42,43]. In India, apart from tribal individuals [44-54], red cell genetic disorders, such as abnormal Hbs, thalassaemia syndrome, and Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, have also been reported in various ethnic groups belonging to Scheduled Castes (SCs), Other Backward Castes (OBCs) and minorities including Muslim, Bohra-Muslim and Jain communities have also been reported in Rajasthan state [55-67]. In fact, this state has two distinct ecosystems arid or desert and humid where malaria is found to be hypo and hyperendemic, respectively.

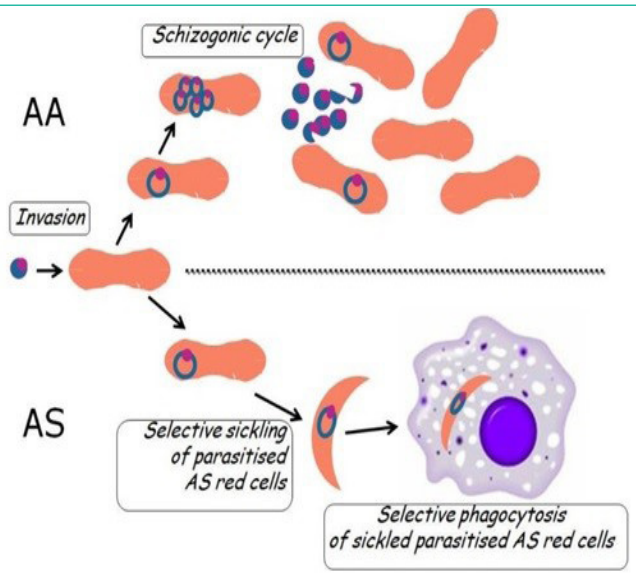

Figure 2: Schematic diagram showing how AS heterozygotes relatively protected from severe *Plasmodium falciparum*-malaria. The upper part of the diagram shows the red cell (erythrocyte) of a normal (Hb-AA) individual suffering from malaria. After the invasion of the erythrocyte by the merozoite, it becomes a ring shape, and then undergoes the schizogonic cycle and release of new merozoites from erythrocytes. The lower part of the diagram shows what happens to the red cell in an AS heterozygote with malaria. The red cell, which appears normal at the time of invasion, undergoes sickling once infected and thus becomes an easy prey for macrophages. Phagocytosis of the parasitized red cells apparently interrupts the schizogonic cycle and thus parasitism can be controlled naturally. Source [19].

Interestingly, these sickle cell genes appear to follow Mendel's laws of inheritance and are distributed accordingly in human or tribal population. Sickle cell gene alleles are commonly found in two forms, the heterozygous (AS) and homozygous (SS) states. In the population, those who are AS heterozygotes have genes for both normal Hb (Hb-A) and sickle cell Hb (Hb-S) and these people live as normal individuals and are protected from malaria but SS homozygotes have the SS alleles and these people have an inherited hemolytic disease, Sickle Cell Anaemia (SCA). This hemolytic disease is usually fatal. There's no cure for most people with sickle cell anaemia. Treatments can relieve pain and help prevent complications associated with the disease.

How do Sickle Cell Genes Protect Tribal People from Malaria?

Based on seminal work confirmed by numerous experimental works, clinical and epidemiological field studies from different parts of Africa covering large population or having large sample size [5], it has been concluded that in AS heterozygotes *P. falciparum*-infected erythrocytes sickle preferentially and are then removed by macrophages by following the phagocytosis mechanism [19]. Furthermore, these studies have also been validated by rigorous statistical analysis [15]. These studies have revealed that AS heterozygotes are more prone to malaria and have a lower number of parasitized erythroctes in their blood. In addition, AS heterozygotes have a lower incidence of two forms of life-threatening severe malaria, cerebral malaria and severe anemia, and very rarely AS heterozygotes die from malaria, even in rare cases when they develop cerebral malaria [12]. These studies also indicate that malarial environments increase the fitness of AS heterozygotes [20].

Interestingly, in protection against malaria, the sickling event has a potential and important role that occurs in AS erythrocytes that had been parasitized (6,68). This indicates that once the malaria parasite has triggered sickling (probably due to deoxygenation and lowering pH caused by the malaria parasite), the sickle cells will be removed by macrophages by a phagocytosis mechanism [10,69]. This sickling-phagocytosis model or mechanism has also been confirmed [27]. No doubt, through this process the parasitemia density or load is relatively reduced in AS heterozygotes [7,8,13,20,27,31]. For easier understanding the sickling-phagocytosis model is also shown in Figure 2. A recent study conducted in Uganda observed that AS heterozygous children (age 1–10) were found to be protected from (i) establishment of blood-stage malaria parasite infection, (ii) development of higher densities of parasites, and (iii) progression of infection to symptomatic malaria [18]. In addition, another reason for protection against malaria is that sickle-shaped erythrocytes create a very unfavorable environment for the development of the malaria parasite, partly due to the low oxygen level. Reduced parasite growth may allow more time for the immune system to respond and destroy infected erythrocytes. In addition, it was confirmed that the malaria parasite, *Plasmodium*, is unable to penetrate or infect the plasma membrane of erythrocytes containing sickle cell haemoglobin (Hb-S) [32]. However, scientists are still working to piece together the exact mechanisms involved in such malaria genetic resistance in humans or tribal people.

Is it Natural Selection Against Malaria in Tribals?

No doubt, in human evolution, it is a complex or unique type of natural selection in tribal people who are living in geographical areas where malarial parasitic disease is more prevalent and hyperendemic. That is, the origin of the sickle cell gene is thought to have resulted from genetic mutation under the pressure of the biological agent malaria. It is well documented that 'natural selection' is the major driving force for the evolution of living organisms [70] and "evolutionary theory" is largely based on an understanding of "selection" and its consequences for the origin of species. The concept of 'fitness' is a central theme of the theory of evolution. The Darwinian concept of selection is now understood in population genetics as the operational force that determines the relative fitness of a genotype in the population, thus affecting the gene concerned [71]. It is also recognized that selection has playing an important role the one hand, in the evolution of living organisms in achieving change in gene frequency by differential survival and reproduction of genotype, and on the other hand, playing a conservative role by producing equilibrium between mutation and selection [72]. One of the best examples for balance polymorphism or natural selection is sickle cell gene (Hb-S) which is more prevalent in tribes inhabiting malaria endemic regions. The AS heterozygote or individual has sickle cell trait (Hb-AS) is protected against *falciparum* malaria and does not suffer from lethal sickle cell anaemia or disease (Hb-SS), whereas the normal homozygote (Hb-AA) is vulnerable to malaria parasite infection [73]. Further it was also confirmed that malaria parasite, *Plasomodium* is unable to penetrate or infect the plasma membrane of red blood cells containing sickle cell Haemoglobin (Hb-S) [68].

Apart from sickle cell gene, G-6-PD enzyme deficiency and beta- thalassaemia genes are also examples of natural selection and are protective factors against the malaria in tribals [74]. The relationship between malaria and these mutant genes has also been investigated and it is now generally accepted that malaria exerts a selective pressure for the maintenance of higher frequencies of sickle cell, β-thalassaemia, and G-6-PD enzyme de-

ficiency genes. In southern Rajasthan (India) where malaria is also hyperendemic, abnormal haemoglobin, such as Hb-C and Hb-SC have also been detected and reported. Though, these genes are less prevalent but their presence in the tribal population has great significance in relation to malaria. The relationship between other abnormal Hb variants and malaria is still unclear or controversial. However, these are, perhaps, due to effect of physical and biological factors of particular geographical region or environment. However, for its justification, more in-vitro and scientific studies are highly suggested.

Sickle Cell Anaemia (Hb-SS) and Fluoride Poisoning in Tribals

In India, especially in rural areas with a high tribal population, almost all drinking groundwater sources are contaminated with fluoride [75-78]. In these areas, thousands of tribal people suffer from chronic fluoride poisoning or hydrofluorosis disease due to the consumption of fluoridated water for both drinking and cooking [79-82]. Neighborhood fluorosis due to long-term industrial fluoride exposure has also been reported in tribals in India [83,84]. It is well established that fluoride damages not only hard tissues (teeth and bones) but also various soft tissues including blood cells. In recent studies, it has been concluded that excess fluoride exposure accelerates various hematological degenerations leading to erythrocyte death and anaemia [85-87]. In tribals, sickle cell disease and β-thalassaemia major are also fatal and cause varying degrees of anemia in tribal adults and children, respectively [25]. Therefore, premature death due to chronic fluoride intoxication is possible in tribal people with these inherited red blood cell genetic diseases. But the attention of the people of the concerned department about this danger has not gone yet, while there is a need for more attention and research.

Conclusion

There is no doubt that malaria is a deadly disease in humans, which is still prevalent and endemic in many countries where tribal populations are also found prominently. Thousands of tribal people live in rural and forest areas where even primary health facilities are not available. Yet these people have been found to be protected from malaria. How can this be possible? Actually, its secret is hidden in the special type of genes present in them. These are called sickle cell genes, which originated during biological evolution due to mutations in genes under malaria pressure. These genes are relatively more prevalent in tribal people and are responsible for the synthesis of sickle cell haemoglobin (Hb-S) and formation of sickle-shaped erythrocytes. In tribal people, these genes are distributed and exist in two forms, the heterozygous (AS) and homozygous (SS) states. Several studies have proved and confirmed that AS heterozygote individuals lead normal lives and are protected from malaria, whereas SS homozygote subjects suffer from the hemolytic fatal disease, sickle cell anemia. This is a kind of "natural selection" in humans. In this only that individual survives (AS heterozygote) who is compatible with nature and is capable of living, otherwise nature automatically eliminates or destroys it (SS heterozygote). In humans, this type of phenomenon also reflects "survival of the fittest" as well as balanced polymorphism in human populations. However, more scientific studies are needed to uncover the exact mechanisms involved in malaria genetic resistance in humans.

Author Statements

Conflict of Interest

There is no conflict of interest of the author.

Acknowledgements

The author thanks to Dr. Darshana Choubisa, Associate Professor, Department Prosthodontics and Crown & Bridge, Geetanjali Dental and Research Institute, Udaipur, Rajasthan 313002, India for cooperation.

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