Research Article

Prevalence of Thalassemia in Nigeria: Pathophysiology and Clinical Manifestations

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Abstract:

There is evidence linking genes for thalassaemia, sickle cell diseases, and glucose-6-phosphate dehydrogenase (G6PD) deficiency to a high prevalence of malaria infection. Haemoglobinopathies are hereditary conditions that mostly results in thalassaemia and sickle-cell anaemia. The current global haemoglobin gene carrier population (i.e., healthy individuals who have acquired only one mutant gene from one parent) is between 1 and 5%. Some haemoglobinopathy genes (alpha-thal, beta-thal and HbS) cause alpha-thalassaemia, beta-thalassaemia and sickle-cell anaemia, respectively. Nigerians have a prevalence of 25–30% for sickle cell anaemia (SCA), G6PD, but both alpha thalassaemia and beta thalassaemia are at the lower limit. Thalassaemia and SCA have comparable clinical manifestations. which is quite prevalent in Nigeria? This could lead to underdiagnosis of thalassaemia, which accompany hypochromia and microcytosis, that could be mistaken for iron deficiency anaemia. Depending on the levels of foetal haemoglobin and haemoglobin A_2, thalassaemia, iron deficiency anaemia, and sickle cell disease continue to be the most common chronic types of anaemia. This review provides details information on the prevalence of thalassaemia in Nigeria and molecular mechanisms in the expression of thalassaemia genes. The authors also suggest various possible way to minimize the occurrences of thalassaemia in Nigeria

1.0 Introduction

Thalassemia is a genetic blood illness that is inherited, manifested by insufficient production of haemoglobin, a protein that is essential to the formation of red blood cells (WHO, 2022). For a form of nourishment, oxygen is necessary for cells to function. There are multiple subtypes of the most common kinds, beta and alpha thalassemia. If beta-globin subunits are produced less frequently than alpha-globin subunits, this results in beta-thalassemia (https://www.who.int/, accessed on December 21, 2023).It is reasonable to speak to thalassaemia as an epidemiological condition given that 60,000 new carriers are born each year and that 1.5% of the world's population is anticipated to be a carrier of the condition (WHO, 2022). In areas where the carrier state is common, two clinically important diseases (HbH disease and Hb Bart's hydrops foetalis) occur in compound heterozygotes and homozygotes. The reason for discussing this here is therefore not because these diseases are rare, rather that they may be rarely considered by physicians outside of the regions where thalassemia commonly occurs. About half of the world's carriers are found in Southeast Asia, with the combined populations of Europe and the Americas making up 10-15% of the total (WHO, 2022). The global distribution of thalassaemia includes the key regions of Africa, Asia, and the Mediterranean where malaria was formerly prevalent. Nigerians who are heterozygote for malaria exhibit similar distributions of the genes linked to malaria.Alpha thalassemia, GPD deficiency, and sickle cell disease are all 25–30% more common in the heterozygote state (WHO, 2020). The similarity in the occurrence of beta thalassaemia trait was discovered very recently. Thus, it's plausible that the underdiagnosis of thalassaemia in the African setting is a result of a lack of appropriate diagnostic resources. It is necessary to talk about these disorders since, despite this, doctors should still take the diagnosis into consideration. Although α-thalassaemia is present throughout the world, its clinical severity is limited. The clinically severe form associated with hydrops fetalis and HbH sickness is most frequently reported in South East Asia, but it is also occasionally observed in the Mediterranean region (Eze, 2022). Two clinically significant illnesses (HbH disease and Hb Bart's hydrops foetalis) affect both compound heterozygotes and homozygotes in regions where the carrier state is prevalent. Deletionsional variants are more common and have less clinical severity than point mutation forms. Currently, the only variant of beta thalassaemia that has been found in Nigerians is the deletion form (WHO, 2022). Upon screening 300 chromosomes for α-thalassaemia, only the -3.7 deletion was discovered, resulting in heterozygote samples in 42% of the samples and homozygote samples in 9% (in press). This implies that Nigerians' thalassaemia is not particularly significant clinically (Oha, 2021). In contrast, although severity varies, beta thalassaemia is almost always clinically severe. As a result,

thalassaemia is categorized clinically as thalassaemia major, intermedia, and minor (1992, Barry). Understanding the nuanced ways in which it may be misdiagnosed requires exploring this topic, as none of the previous study has focused on the prevalence and survival rate between the adult and paediatric categories. This review focuses on the prevalence of thalassaemia in Nigeria, including the pathophysiology and clinical manifestations.

2.0 Epidemiology

As with all other common globin gene disorders (β-thalassaemia and sickle cell trait), α-thalassaemia is highly prevalent in all tropical and subtropical regions of the world (Fig. 1). In certain regions, 80–90% of people may carry the α-thalassaemia gene, nearly reaching fixation (Higgs and Weatherall, 2009). It is believed that every globin gene abnormality, including α-thalassaemia, has been chosen because it protects carriers from the damaging effects of falciparum malaria. This is well supported by micro epidemiological evidence. Although they have been thoroughly investigated, the mechanisms underlying this protection are still unknown. The most prevalent globin condition is α thalassaemia, which causes many people in these regions to have interaction combinations of these variations (e.g. both α and β thalassaemia). Because of variations in how the several molecular abnormalities that cause α thalassaemia interact with one another (Fig. 1)). The Middle East, the Mediterranean, and Southeast Asia are the main regions where HbH illness is prevalent. In the same way, South East Asia is the primary location for Hb Bart's Hydrops foetalis syndrome cases (Harteveld and Higgs, 2010).
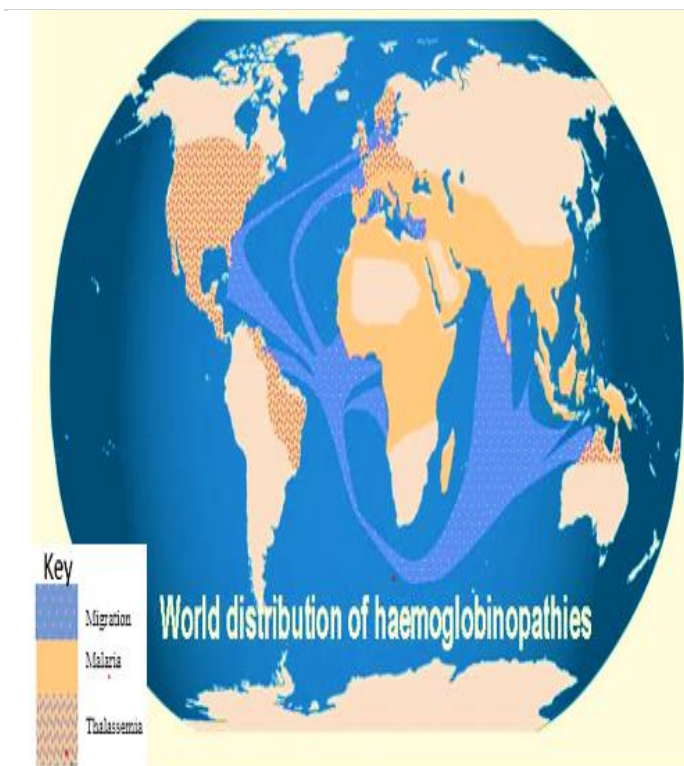

Figure1: The geographic distribution of malaria is overlapped by the global frequencies of hemoglobinopathies.

The slave trade, trading operations, colonization, and historical and contemporary migrant movements have all contributed to the prevalence's rise in formerly non-endemic areas. Thalassaemia is highly prevalent in each of these areas. Natural selection is thought to be the cause of the elevation and maintenance of α thalassaemia carriers' gene frequencies, and they are thought to provide protection against malaria (Modified from Harteveld and Higgs, 2010).

3.0 Prevalence

3.1 Global Prevalence of Thalassaemia

Around 4.4 live births out of every 10,000 worldwide are affected by thalassemia. Because, this disorder has an autosomal pattern of inheritance that does not take gender preference, males and females inherit the relevant gene variants equally. Though not all of these people are symptomatic and some are regarded as silent carriers, while about 5% of people on the planet have a mutation in either the alpha or beta haemoglobin molecule. In actuality, the thalassemia trait—which is caused by gene mutations affects only 1.7% of the world's population (WHO, 2022).

3.2 Alpha-thalassemia

Alpha-thalassemia is more common in some Southeast Asian populations than in others. There is also a significant carrier concentration in the Western Pacific and Sub-Saharan Africa regions. The prevalence of the following people groupings varies by location of the world: Between 0 and 5% of people in the US have thalassemia, and up to 40% of those infected may be inherited carriers. Thalassemia characteristic affects 0-2% of the population in the Eastern Mediterranean region; up to 60% of this group may be hereditary carriers. In Europe, 1-2% of the general population have the thalassemia trait, and up to 12% are inherited carriers. Up to 40% of individuals in Southeast Asia may be inherited carriers of the thalassemia trait, and between 1 and 30% of persons have the trait. 0% of individuals in Sub-Saharan Africa have thalassemia characteristics, and up to 50% may be inherited carriers. In the Western Pacific, 0% of people have thalassemia trait, and up to 60% may be hereditary carriers (WHO, 2022). In Nigeria, there is only one form of single alpha globin gene deletion (-alpha 3.7) that causes the alpha-thalassaemia determinant. Similar tendencies to those described in Jamaican and American studies were observed when comparing the haematological aspects of sickle-cell disease patients with (-alpha/alpha alpha, -alpha/-alpha) or without (alpha alpha/alpha alpha) alpha-thalassaemia. Nonetheless, our research indicates that, in contrast to many other African groups, the frequency of alpha-thalassaemia in Nigerian individuals with or without homozygous sickle-cell disease (AA, AS, and AC genotypes) is the same (0.24). (WHO, 2022).

3.3Beta-thalassemia

The most prevalent type of thalassemia in the population of Mediterranean, African, and South Asian ancestry is beta-thalassemia. In America, the gene mutation affects about 0-3% of the population, while 2-18% of the population in the Eastern

Mediterranean were affected. In Europe, about 0–19% of the population have thalassaemia gene mutation. In Southeast Asia, the gene mutations affect up to 0–11% of the total population, while about 0-12% of the population in Sub-Saharan Africa were affected. In the Western Pacific, a gene mutation affects 0–13% of the population. In tropical and subtropical regions, especially those with malaria endemic are more likely to have both alpha- and beta-thalassemia (WHO, 2018). The exact cause of this link is unknown, but carriers of the genetic mutation are thought to be better protected against malaria. The most likely areas in Europe to be affected are southern regions of Italy and Greece. The Maldives has the highest rate of thalassemia in Asia, with 16% of the population reporting having the disease; rates are significantly higher in Thailand and India, two more tropical nations. All kinds of thalassemia have the potential to be fatal in rare cases, particularly if multiple genes are faulty and impair the formation of the globin chain. Less than 36,000 deaths were documented in 1990 due to thalassemia; in 2013, 25,000 deaths were caused by the condition (WHO, 2020). It is distributed irregularly throughout Greece and Italy but is present throughout the Mediterranean. It is less frequent in the western Mediterranean and doesn't seem to be very common in France, with the exception of those who are Italian or Spanish in origin. However, the disease is common throughout western Asia and the Middle East, and it is probably the most common inherited hemoglobin disorder in India. Although sickle cell disease is assumed to prevail among hemoglobinopathies in places south of the Sahara, thalassaemia is expected to affect 3-7% of people in most of North Africa (Kwiatkowski, 2015). Nigeria is a country with a higher prevalence of beta thalassaemia, despite the possibility that some people are quiet carriers of the trait. Because alpha thalassaemia is highly prevalent in the same environment, its existence might have been obscured. It is therefore necessary to consider beta thalassaemia trait as a differential diagnosis in individuals who appear with haemolytic anaemia in this environment (Kotila, 2013).

4.0 Synthesis of Haemoglobin and Globin genes

The tetrameric molecule known as haemoglobin (Hb) is composed of two alpha-like (ζ or α) and two beta-like (ε, γ, δ or β) globin chains. Each globin chain has a heme group linked to it, which functions as an oxygen carrier protein in red blood cells (Kwaifa et al., 2015). One erythrocyte contains about 250 million haemoglobins (Jane et al., 2015). The alpha globin gene cluster, also known as 5′-ζ-μ-α2-α1–3′, is located in the short arm of chromosome 16 (16p13.3). Alpha globin gene clusters are grouped based on the sequence in which they express themselves during the developmental stage. Conversely, the beta-globin gene locus is found at 5′-ε-Gγ-Aγ-δ-β-3′ on chromosome 11 (11p15.5) (Mettanada et al., 2018). Hb Gower-I (ζ2ε2), Early in the embryonic life, Hb Gower-II (α2ε2) and Hb Portland (ζ2γ2) are synthesized, along with foetal haemoglobin (HbF, α2γ2), which is the predominant form throughout the foetal life. Foetal haemoglobin changes postnatally to HbA$_2$ (HbA$_2$, α2δ2) and HbA (α2β2) (96–98%) (Fig. 2) (Kwaifa et al., 2020).

Genes for alpha-globin are regularly expressed at high quantities from the start of foetal development. Therefore, throughout the foetal and adult life, the impacts of mutations in the α-globin gene are evident. This is a significant distinction from β-globin gene mutations, which manifest their impact only about half a year after birth. According to Kwaifa et al. (2020), the overall synthesis of beta-globin chains originating from the two beta-globin genes on chromosome 11 is estimated to be equivalent to the combined production of alpha-globin chains produced by the four alpha-globin genes on chromosome 16.
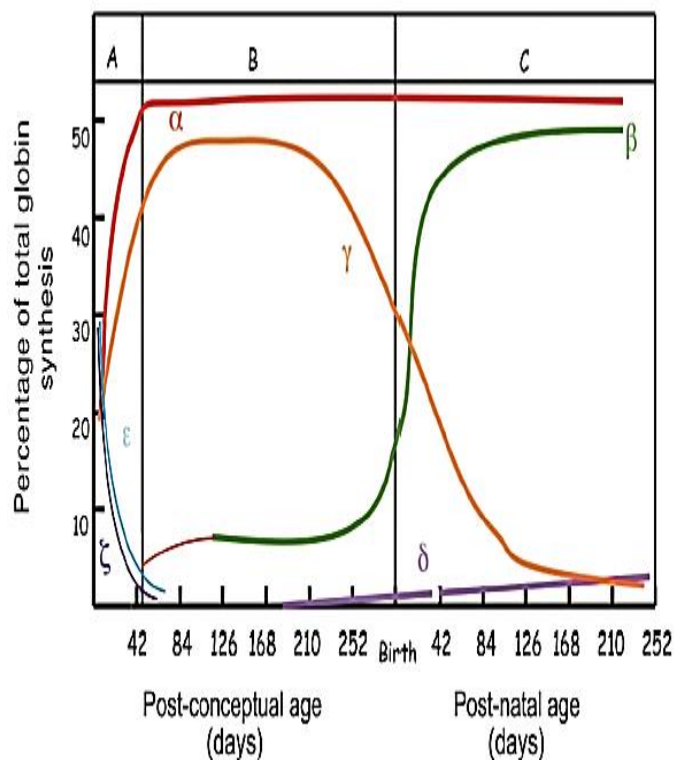

Figure 2: The Developmental Stages of Haemoglobin Production

The x-axis shows the foetus's or baby's age in days, while the y-axis shows the proportion of all globin genes that are expressed. The birth time is shown by the vertical lines. The first 42 days of gestation are when the embryonic genes and the ε-to-γ-globin gene transition occur. Soon after birth, there is a second flip from γ-to β-globin (Modified from Kwaifa et al., 2020).

4.1 Mechanisms of globin Gene Expressions

Understanding the molecular basis of thalassemia needs thorough knowledge of the molecular mechanisms that coordinate and control the expression of the alpha and beta-globin genes. Four regulatory elements called enhancers, which are situated 10–48 kilobases upstream of the genes, regulate the production of alpha-globin. These enhancers have underlying sites of DNase 1 hypersensitivity and are commonly referred to as multispecies conserved sequences (MCSR1-4). Of these enhancers, MCS-R2 (HS-40) was revealed to be the most effective regulatory enhancing factor for the synthesis of alpha-globin (Kwaifa et al., 2020). The expression of alpha-globin genes is initiated during erythroid differentiation through the demethylation of repressive chromatin signatures in conjunction with promoter genes. Transcription factors of the

erythroid, including GATA-binding factor 1 (GATA1), nuclear factor erythroid 2 (NF-E2), stem cell leukaemia pentameric complex, and Kruppel-like factor1 (KLF1) are subsequently bound to the enhancers to boost alpha-globin gene expression (Vernimmen, 2018). Similarly, five enhancers of the β-globin genes, known as the locus control regions (LCR) have been discovered (Mettanada et al., 2018). These are associated with erythroid transcription factors, such as LIM domain-binding protein 1 (LDB1), GATA1, Friend of GATA1 (FOG1), KLF1, NF-E2, and stem cell leukaemia (SCL) factor on the β-globin promoter, as well as active chromatin signatures (H3K4me3 and H3K27me3). The B-cell lymphoma protein, sometimes referred to as leukaemia 11A (BCL11A), is one of the transcriptional repressors of γ-globin that is thought to be the most efficient in controlling the haemoglobin switching. According to Bauer et al. (2012) and Zhou et al. (2010), erythroid transcription factor KLF1 is also known to have a role in globin switching by directly activating the beta-globin genes promoting the synthesis of the γ-globin silencer BCL11A. Others include the haematopoietic transcription factor MYB which was discovered to suppress the γ-globin transcription in various ways by activating TR2/TR4 and KLF1(Mettanada et al., 2018). Leukaemia/lymphoma-related factor (LRF) has been identified as a powerful suppressor that can partially repress the γ-globin genes in recent times (Masuda et al., 2016; Smith and Orkin, 2016).

5.0 Pathophysiology of Thalassaemia

The blood condition thalassemia is brought on by DNA mutations in the cells that make haemoglobin. Reduced red blood cell production and ability to carry oxygen throughout the body may cause fatigue and other symptoms. Haemoglobin is made up of an iron-based heme ring with two alpha and two beta (or gamma) globin chains. Which type of thalassemia a person has depends on the amount of defective genes and the percentage of mutated beta or alpha hemoglobin molecules (Schrier, 2002).

5.1 Alpha-Thalassemia

Alpha-thalassemia results from both insufficient production of alpha-haemoglobin chains and an excess of beta chains. Four genes on chromosome 16—two of which are inherited by each person's parents—produce the alpha region of hemoglobin. The severity of the ailment is correlated with the number of gene mutations in the following way:

➢ A solitary gene mutation has the potential to induce the disease in progeny as a silent carrier with no obvious symptoms.
➢ Two gene anomalies causing moderate indications and symptoms are called alpha-thalassemia minor or alpha-thalassemia characteristics.
➢ Three gene anomalies produce haemoglobin H sickness, often known as alpha-thalassemia intermedia. The disorder presents with moderate to severe symptoms.

➢ Often fatal before or shortly after labor, hypodrops fetalis or alpha-thalassemia, also known as major, are caused by these four gene defects (Schrier., 2002)

5.2 Beta-Thalassemia

Beta-thalassemia is caused by an excess of alpha chains and insufficient synthesis of beta-haemoglobin chains. Two genes on chromosome 11—one inherited from each parent—produce the beta component of the haemoglobin chain. The number of gene mutations and the severity of the condition are associated in the following ways:

➢ Alpha-thalassemia trait, commonly referred to as beta-thalassemia minor, is a hereditary disorder with mild signs and symptoms.
➢ There are two gene defects that produce beta-thalassemia major, also called Cooley's anemia, which causes moderate to severe symptoms (https://www.mayoclinic.org/diseases-conditions/thalassemia/symptoms-causes/syc-20354995).

5.3 Molecular basis of Common Variants of Thalassaemia, including Non-Deletional Type of Alpha Thalassaemia

More than seventy types of non-deletional mutations causing thalassaemia have been found and recorded. Point mutations that impact genomic areas essential for the regular expression of α-globin genes are classified as non-deletional mutations. The expression of the α-globin genes seems to be more significantly impacted by point mutations that affect the α_2-globin gene. In typical conditions, the expression of the α_2-globin gene is nearly three times greater than that of the α_1-globin gene (Kwaifa et al., 2020). Non-deletional mutations can produce unstable haemoglobins, which typically precipitate in red blood cells, form insoluble inclusion bodies, and ultimately cause the membranes of the red blood cells to become damaged or destroyed. Hb Constant Spring, αIVS1(−5nt) α, the Hb Icara, Hb Koya Dora, αTSaudiα, poly-A α_2, Hb Quong Sze, Hb Seal Rock, Hb Bibba, Hb Chesapeake, Hb M-Boston, Hb Pakse′ as Hb Dartmouth, Hb Quong Sze, Hb Evora, Hb Heraklion, Hb Adana, Hb Aghia Sophia, Hb Petah Tikva, and Hb Suan Dok are a few examples of non-deletional mutations of the HBA$_2$ at termination codon. All of them affect the coding sequence's stop codon at position 142, which results in a prolonged α-globin chain and, ultimately, an exceedingly unstable Hb variant (Karakas et al. 2015). The cellular processing of an unstable mRNA, which has a shorter life span, or the precipitation of an unstable Hb variant in red blood cells leading to haemolysis could be the molecular basis of instability and lower expression of α-globin genes (Fucharoen and Viprakasit, 2009). Anaemia and haemolysis are the hallmarks of oxygen deprivation because unstable Hb variations may not interact with other Hb molecules but instead have a high oxygen affinity that reduces the amount of oxygen that reaches the tissues. These would result in extramedullary erythropoiesis in the bone, liver, and spleen due to dyserythropoietic marrow enlargement (Kwaifa et al., 2020).

5.3.1 Haemoglobin constant spring (Hb CS)

The most prevalent kind of non-deletional mutations seems to be Hb Constant Spring, which arises from the mutation of a "stop" codon (α142, Term→Gln, TAA− CAA in α2). A glutamine molecule is introduced in this state. Thus, it results in the synthesis of an α-globin chain with additional amino acid residues rather than the cessation of the chain formation (Kwaifa et al., 2020). This leads to an imbalance that makes it easier for globin chains to bind, which makes red blood cells unstable. These red blood cells frequently exhibit an aberrant MCV, which is indicative of dehydration (Singer., 2009). With an estimated 1–2% of total Hb in the heterozygote state, the concentration of Hb CS in the blood is significantly lower. The manifestations of homozygous Hb CS and thalassemia intermedia may be comparable (Singer., 2009). Along with Hb H illness, this disorder was initially identified in a Chinese family in Constant Spring, Jamaica (Kwaifa et al., 2020). Reports of Hb CS were common in China, the Mediterranean, and South East Asia. Up to 10% of cases were reported in northeastern Thailand (Singer., 2009)., and 5-8% in southern China (Kwaifa et al., 2020). In Malaysia, the prevalence rates of Hb CS among the Malay, Chinese, and Indian populations are 2.24, 0.66, and 0.16%, respectively. t was also found in the population of "Orang Asli," or aborigines, in West Malaysia (Kwaifa et al., 2020). Hb CS seems to be the most prevalent α-globin chain variant in South East Asia overall, with Hb QS—which is comparatively uncommon—found in Malaysia and Singapore (Viprakasit et al., 2004).

5.3.2 HbH-constant spring (HbH-CS)

A well-known non-deletional α-thalassaemia, haemoglobin H-Constant Spring is typified by the combination of α0 and Hb CS (−−/−αCS). HbH-CS often manifests as moderate anaemia. However, there have been reports of severe foetal anaemia linked to hydropic characteristics and extremely complex haemolysis predisposing to acute haemolysis (Kwaifa et al., 2020). Furthermore, 145 paediatric patients with HbH Constant Spring were analysed, and the results showed that there is a wide range in the clinical severity of this illness. Since many of these individuals required frequent transfusions, had lower baseline haemoglobin levels, and had undergone splenectomy by the time they were six years old, they were categorized as having a more severe phenotype. On the other hand, patients who have the same genotype could exhibit severe traits and need close supervision. Several HbH-CS patients compensated fairly well, exhibiting normal pubertal development and growth, and did not require regular transfusions or splenectomy (Fucharoen and Viprakasit, 2009). Due to the amount of unstable αCS mRNA in circulation and the lowered Hb H-CS level, Hb electrophoresis is particularly difficult to detect HbH-CS. Due to extreme sensitivity to oxidative stress, an individual with Hb H-CS typically develops cholelithiasis, splenomegaly, recurring drops in haemoglobin, and frequent severe anaemia. Regular blood transfusions, genetic counselling, education campaigns regarding the related risks, and timely monitoring of potential complications are all important components of clinical care for patients with Hb H disease, particularly those with Hb H-CS (Kwaifa et al., 2020).

5.3.3 Haemoglobin Quong Sze (Hb QS)

The HBA2-globin gene causes a less common kind of non-deletional mutation called Hb QS, in which proline is replaced by the amino acid eucine (CTG → CCG, codon 125), resulting in an elongated α-globin chain. Mild to moderate haemolysis and membrane malfunction are also present in patients with this illness (Singer., 2009). Any unstable haemoglobin variation, known as Hb QS (HBA2 c. 377 T > C), is primarily found in Southern China and Thailand. In the Chinese population, it is one of the main alleles that causes non-deletional Hb H (β4) (Kwaifa et al., 2020).

5.3.4 Haemoglobin (Hb) Paksé

A rare kind of non-deletional α-thalassaemia known as Hb Paksé is caused by mutations at the HBA2-globin gene's termination codon (TAA → TAT), which produce an extended polypeptide. It is typically found in Thailand's central region. Low haemoglobin levels in these patients typically result in mild to moderate anaemia, as well as low MCV, MCH, and RBC counts (Viprakasit et al., 2004).

5.3.5 Poly-adenylation (poly a) signal mutations

Variable base substitutions or deletions on the HBA2-globin gene result in poly A signal mutations. Greece, Saudi Arabia, and Turkey have very high rates of these mutations. A prolonged polypeptide is the outcome of these mutations, which are likewise linked to the termination codon of the HBA2-globin gene (Viprakasit et al., 2004).

5.3.6 Haemoglobin (Hb) Koya Dora

The low incidence of Hb Koya Dora is caused by mutations in the HBA2-globin gene's termination codon, which result in an elongated polypeptide. According to reports, Hb Kaya Dora is population-specific; in the Koya Dora tribe of Andhra Pradesh, India, incidences of 10% have been recorded (Fucharoen and Viprakasit, 2009). This Hb variation is unstable and can precipitate on the membrane of red blood cells, leading to haemolysis and inefficient erythropoiesis (Fucharoen and Viprakasit, 2009).

5.3.7 Haemoglobin (Hb) Chesapeake

Hb Chesapeake was initially identified in 1966 as a very rare but oxygen-affinity (Kwaifa et al., 2020) bacterium. having a single α-chain substitution, it is an anomalous haemoglobin having the molecular formula α292 Arg → Leuβ2A. Since this haemoglobin has a higher affinity for oxygen, the heterozygous variants are linked to polycythaemia, presumably as a compensatory measure for the decreased oxygen release in the tissues. The amino acid responsible for the α1-β2 chains interaction is affected by this loss, which also modifies the rotational transition that typically takes place between the oxygenated high-affinity state and the deoxygenated low-affinity state. As a result, hypoxia and compensatory erythropoiesis result from the prevention of haemoglobin in the high-affinity relaxed state. Although they can have

musculoskeletal (joint) pain, patients with haemophilia Chesapeake are expected to have normal life. German and Irish lineages, as well as Japanese, French, and Afro-American families, have significant frequencies of Hb Chesapeake (Kwaifa et al., 2020).

5.3.8 Haemoglobin (Hb) ADANA

At codon 59 of the HBA1 or HBA2-globin gene (GGC → GAC), haemoglobin Adana is a form of non-deletional alpha thalassaemia mutation that results in Gly → Asp substitution (Cürük., 2007). A glycine excess at a position in the E helix that is tightly linked to a glycine residue in the B helix is involved in this substitution. The stability and integrity of the cell's molecule are drastically altered by this substitution, which results in aberrant precipitates on the red cell membrane, which induce haemolysis and inefficient erythropoiesis (Kwaifa et al., 2020). According to reports, this mutant variation is associated with a common α1-thalassaemia deletion [−(alpha) 20.5 kb], which causes anaemia and a severe form of Hb H illness. In addition, it is marked by an increase in Hb Bart's, a drop in HbA2 levels, an increase in Zeta chain, and a hint of HbH illness. Because carriers of Hb Adana may have normal haematological markers, the examination for this condition is quite challenging (Kwaifa et al., 2020). Alpha-globin gene sequencing or PCR-based amplification refractory mutation system testing are two methods used in laboratories to identify Hb Adana (Singh et al., 2018). A combination of Hb Adana and other α-globin deletions can result in a variety of phenotypes, from moderate anaemia (e.g., −α3.7 and −α4.2) (Kwaifa et al., 2020) to a more severe HbH-like disease (− − 20.5 and −α4.2-QT (Q-Thailand) (Tan et al., 2016). Severe Hb H-like phenotypes (e.g., α_2CS [Constant Spring], α2Paksé, α2IVS-II-142, α2IVS-II, α2codon24, α2codon22, and rSNP 149,709 T > C) are typically associated with Hb Adana HBA2 point mutations that co-inherited with a single α1 non-deletional mutation (Tan et al., 2016). Countries like Saudi Arabia (11.6%) (Chen et al., 2000) and Indonesia (16%) have a greater prevalence of Hb Adana, whereas Turkey (0.5–0.6%) (Bozdogan et al., 2015), Iran and Iraq (1-2.5%, and China (1%%) (Akbari and Hamid., 2012) have lower incidences (Nainggolan et al., 2013). A range of 1.4% to 21.4% was reported in different Malaysian reports (Yatim et al., 2014).

5.3.9 Haemoglobin (Hb) G Philadelphia

A mutation at codon 16 of the HBA1-globin gene (AAG–→GAG) resulting in the substitution of glutamic acid for lysine causes Hb G-Philadelphia, a stable and normally functioning oxygen carrier. It migrates more quickly at alkaline pH than normal haemoglobin (HbA) and has a lower isoelectric point than HbA. Similar to HbH, Hb G-Philadelphia migrates at an acidic pH along with HbA (Arya et al., 2009). It was originally found in an Afro-American family by Rucknagel et al. in 1955 (Kwaifa et al., 2020). The most common α-chain variant in the United States of America (USA) is Hb G-Philadelphia, which is found among people of African heritage and has a carrier rate of about 1 in 5000. It was later discovered in several racial and ethnic groupings, such as Asians, Caucasians, and Africans.

Additionally, Sardinians, Indians, Italians (from Northern Italy), and a few Chinese families have it (Arya et al., 2009). The homozygous variant of the Italian/Mediterranean mutation, which affects a normally functioning α-globin gene, is not harmful. One mutant gene is its trait, and it is absolutely silent. According to genetic research, the AG-P locus is typically the only functional locus present on the chromosome in question. On the other hand, the quantity of Hb G-P increases to around 45% when α2-thalassaemia (3.7 kb deletion) occurs in trans (−αG/−α); this person may have a unique microcytosis and hyperchromasia (α_2-thalassaemia) (Arya et al., 2009). Additionally, these patients may be homozygotes for α2-thalassaemia with unique microcytosis and hyperchromasia (Table (Table3).3). Although exceedingly rare, Hb H illness (−αG/−−) with 100% Hb G-Philadelphia is caused by the combination of α1-thalassaemia and Hb G-Philadelphia. It is quite typical for Hb G-Philadelphia (−αG/αα) to co-inherit with Hb S and/or Hb C. Individuals who possess all four α-globin genes (αGα/αα) and 20–25% Hb G-Philadelphia without any haematological abnormalities are considered to be Hb G-Philadelphia patients (Arya et al., 2009).

6.0 Clinical Manifestations of Thalassaemia

Clinical manifestation of thalassemia includes:

- Anaemia
- Failure to thrive in early childhood
- Leg ulcers
- Jaundice, usually slight, gallstones
- Bone abnormalities
- Hepatosplenomegaly, which may be massive; hypersplenism
- Abnormal faces, prominence of molar eminences, frontal bossing, depression of bridge of the nose and exposure of upper central teeth
- Generalized skeletal osteoporosis
- Fractures due to marrow expansion and abnormal bone structure
- Skull radiographs showing hair on end appearance due to widening of diploic spaces.

Individuals suffering with thalassemia face several challenges. The participants' different variations in hemoglobin, their levels of HbF and HbA2, and the mean and standard deviation of the hemological data. Evidence has been found to associate the prevalence of malaria infection with the genes for thalassemia, sickle cell disorders, and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Principal complexities consist of:

Heart: Heart issues are the main cause of death in thalassaemia major, resulting from iron overload. Heart conditions are less common in thalassaemia intermedia patients with less severe hemosiderosis. The majority of patients experience permanent pericardial changes, valve problems, and congestive heart failure as cardiac repercussions. Pulmonary hypertension is another common cause of secondary right heart failure (Glickstein, 2016).

Thromboembolic side effects: These are typical in thalassaemia, and in thalassaemia intermedia, they are four

times more common than in major. There are more venous events in thalassaemia intermedia and more arterial events in thalassaemia major. Certain ideas suggest that the phospholipids visible on the surface of the wounded circulating red blood cells have a procoagulant effect, which could be the reason for the chronic hypercoagulable state (Glickstein, 2016). *Endocrine*: Endocrine disorders are less common in thalassaemia intermedia than in thalassaemia major; nonetheless, the incidence of these problems varies greatly, contingent upon the degree of iron overload and the severity of anemia. Hypogonadism is the most prevalent endocrine issue, affecting female patients at a higher rate than male ones. The conditions that come next include diabetes and hypothyroidism, which are found in 5.7% and 24% of individuals with thalassaemia intermedia, respectively. Delays in puberty and irregular menstruation are not uncommon. Over 50% of males with thalassaemia have oligospermia or azoospermia (Pignatti-Borgna, 2017). There are many difficulties associated with pregnancy. *Bone illness:* Osteoporosis is a common cause of morbidity in people with thalassaemia, with a prevalence of up to 50% (Borgna-Pignatti, 2017). Low bone mineral density and vitamin D insufficiency are associated with this. It is sometimes associated with pathological fracture, which is more common in mid-adulthood among individuals with thalassaemia major. Endocrine issues, slow bone growth, iron and desferrioxamine toxicity, and liver disease are all linked to the complex process of osteoporosis in thalassemia patients.

6.1 Some Common Complications of Thalassaemia

Because the causes of thalassaemia are complexes, some of the common complications include, infertility (Fig. 3).
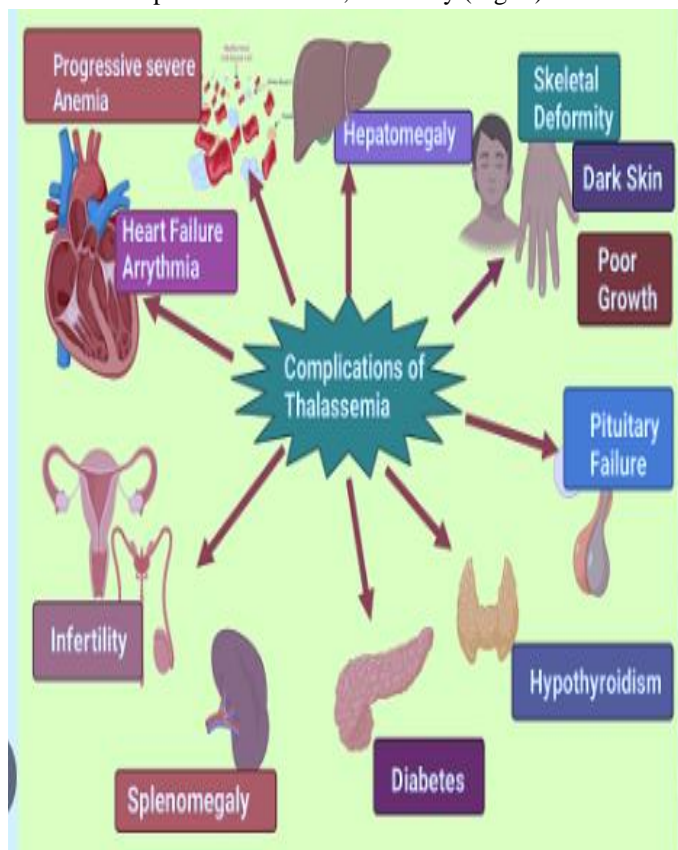

Figure 3: Some Complications of Thalassaemia. (WHO, 2022)

7.0 Options for Treatment

Blood Transfusion: Although those with thalassaemia intermedia do not require blood transfusions, those with thalassaemia major do. The most difficult therapeutic choice to be made when treating a patient with thalassaemia intermedia is whether or not to begin a chronic transfusion program (Borgna-Pignatti, 2007). Sometimes an infection that results in an aplastic crisis calls for transfusions. The medullary and extramedullary tissues hypertrophy when transfusion is withheld. It should be noted that a transfusion regimen initiated in childhood to support development can be discontinued after adolescence. Conversely, some persons who have not had a blood transfusion in two or more decades may gradually develop severe anemia and require regular transfusions.

Chelation: The human body cannot get rid of excess iron on its own; iron chelators are the only effective method for doing so. When the chelating medication deferoxamine was initially developed in the 1960s, it was injected intramuscularly before being changed to a subcutaneous infusion. This marked a substantial improvement in terms of increasing survival and reducing issues (Borgna-Pignatti, 2007). Deferiprone and deferasirox, two oral chelators, have lately made therapy easier to administer and more successful. Despite the switch to oral medication, compliance remains a problem that hinders the effective prevention of iron excess. The oral active chelators seem to be more effective in binding labile iron, lowering the generation of reactive oxygen species, and gaining access to the chelatable iron pool of cardiomyocytes (Borgna-Pignatti, 2007).

Transplantation of Stem Cells: Patients may be candidates for haemopoietic stem cell transplantation whether their donor is related or unrelated and has the same HLA. The likelihood of recovery varies when receiving grafts from unrelated donors, ranging from 80-85% to 90-95%; however, in these situations as well, the likelihood reaches 90% when donor matching is as stringent as it is between HLA identical siblings (Toumba, 2010). Transplant-related mortality averages 5% even in the best of circumstances, therefore it is probably only worth taking a chance in cases of very serious transfusion-dependent sickness (Toumba, 2010).

Gene therapy is a potential thalassemia treatment that could take the place of bone marrow transplantation and conventional therapy. Retroviral vectors containing the human globin cassette are unstable and exhibit low expression, which is one of the numerous challenges associated with gene therapy. Significant progress has now been made in developing viral vectors that transport the -globin expression cassette steadily (Toumba, 2010).

Recombinant Human Erythropoietin (rHuEPO) can raise hemoglobin levels in some thalassaemia intermedia patients, however the medication's cost is high, the impact is very temporary, and the subcutaneous delivery is inconvenient. According to Toumba (2010), the most often administered dose is five to ten times greater than the amount for anemia in chronic renal failure. Patients with thalassemia benefit just as much from other sickle cell disease treatments. It has been discovered

that in thalassaemia patients, HbF reactivation by 5 azacytidine, Butyrate, and Hydroxycarbamide (Hydroxyurea) is similarly effective.

Antioxidant therapy is commonly given to patients with thalassemia since it is believed that oxidative damage contributes significantly to the cell damage that these people experience. Patients with thalassaemia are also recommended to take folic acid every day due to increased erythropoiesis, which results in higher folate usage (Toumba, 2010).

8.0 Survivability

Once a disease mostly affecting children, thalassemia has caused patients' median ages to rise as a result of increased survival and a drop in the birth rate. Individuals who undergo regular transfusions and the appropriate chelation therapy survive longer than those who do not, usually dying before they reach their second or third decade (Haidar, 2010). Heart issues account for 71% of deaths in people with thalassaemia major. It has been demonstrated that population screening, genetic counseling, and prenatal diagnosis are all highly effective in treating the condition (Haidar, 2011).

Ways Forward

According to the study, thalassemia is a serious hereditary haemoglobin illness that is misdiagnosed in this region of the world, particularly when it manifests with significant symptoms like chronic anaemia. Complete blood counts (CBC), peripheral blood film examinations, haemoglobin electrophoresis, isoelectric focusing, quantification of haemoglobin A_2 and haemoglobin F, and genetic testing can all point to a thalassemia diagnosis. However, for this investigation, easily available methods for measuring haemoglobin A_2, haemoglobin F, haemoglobin electrophoresis, and CBC were used. Additionally, it should be noted that while molecular methods are currently used to diagnose thalassemia, their use is restricted to confirmation after HbA2 quantification and HbF level estimation, as well as the handling of difficult cases. Adults and children with chronic anemia should be screened for alfa and beta-thalassemia based on diminished red cell indices and elevated levels of HbF and HbA2. HbF and HbA2 levels along with red cell indices remain a reliable diagnostic tool for thalassemia diagnosis as long as the right diagnostic methods are applied.

Conclusion

The study discovers that thalassaemia is underdiagnosed in African contexts, such as Nigeria, even though the genes causing the disease are among those connected to malaria infection. Various reason has been implicated to the decreased prevalence of thalassaemia in Nigeria: First among the reasons for this is because it presents in a manner comparable to sickle cell illnesses, which are highly common in the environment. Secondly, it could be mistaken for iron deficiency anaemia due to the prevalent association with hypochromic microcytic anaemia. Additionally, genetic study confirmation, particularly in a proposed epidemiologic area is limited in Nigeria and is associated with the decreased figure for the incidence of thalassaemia in Nigeria. Further molecular tests are advised to determine the mutations causing the thalassemia-like traits (increased HbA_2 and HbF) in these patients who have already experienced chronic anaemia.

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