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REVIEW ARTICLE

Prevention of hemoglobinopathies in Saudi Arabia: efficacy of national premarital screening and the feasibility of preimplantation genetic diagnosis

Muhammad Umair[1], Majid Alfadhel[1,2*]

ABSTRACT

Hemoglobinopathies constitute the most frequent, inherited single-gene disorders. Its prevalence is increasing substantially and might cause a substantial economic burden on affected families and countries. The current study findings recommend population screening strategies to be implemented for severe disorders such as sickle-cell disease, hemoglobin E disease, α- and β-thalassemia, and normal individuals to identify the carrier status and manage the disease pathogenesis. In addition, national registries should highlight the information and contribute to the proper management and care of patients suffering from hemoglobinopathy. Furthermore, the Saudi Government should provide a conceptual framework to determine the specific preventive strategies to manage the incidence of hemoglobinopathies effectively.

Keywords: Hemoglobinopathies, sickle cell, α-thalassemia, newborn population screening, β-thalassemia.

Introduction

The hemoglobinopathies are characterized as a diverse group of genetic disorders associated with hemoglobin (Hb) synthesis and a frequent disorder worldwide. Each year, an estimated 400,000 newborns are born with this severe disorder. There is a significant variation in the disorder's geographic prevalence, as most cases are reported from the Middle East, Mediterranean countries, Southeast Asia, Indian subcontinent, and Sub-Saharan Africa (1). Hemoglobinopathies mostly result from quantifiable imperfections in the Hb, also known as the thalassemias and the Hb structural variants. The clinically substantial types include α- and β-thalassemia, HbC disease, HbE disease, and sickle-cell disease (SCD) (1). The exact clinical picture in such a situation is mostly determined with the help of an underlying genotype. The phenotype can vary in presentation from silent carrier to a calm state and from moderate to severe anemia (lethal) (3,4). In thalassemias, a complete blood count (CBC) is the primary screening method as it presents a hypochromic microcytic red cell. Thus, a mean Hb cell concentration value of <27 pg and a mean cell volume value of <79 fL are calculated to identify the carrier status. However, these values may not show abnormality in the case of compound heterozygous states of silent α-thalassemia and α- and β-thalassemia (4).

This study extends the knowledge by updating the recent trends in the occurrence of hemoglobinopathies. Such a study might help researchers to evaluate the existing hemoglobinopathy screening program effectiveness and generate future research ideas. Furthermore, this might lead to decision-making and implementation of public policies regarding the pathophysiology of hemoglobinopathy-related growing list of disorders.

Hematologic System

The hematologic system is crucial in the human body. It performs vital functions such as the delivery of oxygen and nutrients to tissues, the removal of toxic byproducts, the maintenance of the immune system against pathogens, and the provision of hemostasis under challenging situations such as trauma. The present review provides an overview of hemoglobinopathies and highlights clinical pearls, current perspective for proper patient's management, and future perspectives.

Correspondence to: Majid Alfadhel
*Genetics Division, Department of Pediatrics, King Abdullah Specialized Children's Hospital, King Abdulaziz Medical City, Riyadh, Saudi Arabia.
Email: dralfadhelm@gmail.com
Full list of author information is available at the end of the article.
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Prevalence of Hemoglobinopathies in the Middle East Region

The Arab speaking world comprises 22 different countries, and the carrier rate and the prevalence of hemoglobinopathies vary widely among these countries. It ranges from 1% to 58% in the case of α-thalassemia and 1% to 11% in the case of β-thalassemia, whereas the incidence rate for SCD is reported as 0.3%-30% (5). Recessive hemoglobinopathies (homozygous or compound heterozygous mutations) are mostly caused by consanguineous marriages that might increase the incidence rate as high as 60% (5). The prevalence of SCD and β-thalassemia is considered to be one of the highest in Saudi Arabia than the surrounding Middle East countries (0.05% and 4.50%, respectively) (6)._Several programs, such as newborn screening and prenatal screening, mainly focus on premarital screening and are currently carried out in different countries (Table 1). Several countries have deemed compulsory Premarital Screening and Genetic Counseling Programs (PMSGCs) such as the Gaza Strip (7), Saudi Arabia (8), Lebanon (9), Jordan (10), Iran (11), and the Kurdistan region in Northern Iraq (12). The national thalassemia-screening program in Turkey offers premarital screening voluntarily to couples in 33 different provinces in the specific areas, where hemoglobinopathies are prevalent, which resulted in a 90% reduction in the number of affected births (13). The 6-year outcome of the Saudi PMSGC estimated that of all the cases examined, 4.5% of men and 1.8% of females were carriers. There was a constant prevalence for SCD (45.1 per 1,000), whereas the prevalence for β-thalassemia showed a decrease (32.9-9.0 per 1,000) (14).

Table 1. *Countries in the Middle East rand Mediterranean and regions with mandatory hemoglobinopathy screening programs.*

S.No.	Region	Implementation year
Middle East		
1	Saudi Arabia	2004
2	Iran	1997
3	Palestinian territories	2000
4	Turkey	1995
5	Jordan	2004
6	Bahrain	2005
7	Iraqi Kurdistan	2008
8	United Arab Emirates	2011
Mediterranean		
9	Cyprus	1973
10	Italy	1975
11	Greece	1975

Erythrocyte Disorders

According to the World Health Organization, anemia is defined as when "hemoglobin (Hgb) is less than 13 g/dl" in the adult male and less than "12 g/dl" in adult non-pregnant female (15). The prevalence of different anemic disorders is approximately 12% in male (adult), 30% in non-pregnant female (adult), and 24% in the old male/female (16). Furthermore, the prevalence of anemia is observed higher in patients preparing for surgery (17). Several types of anemia exist or coexist in preoperative patients. However, iron deficiency is the most common type (16).

Thalassemia Syndromes

Thalassemia syndromes constitute a group of recessive genetic disorders mostly characterized by the absence or decrease of the specialized globin subunit. Broadly, thalassemia syndromes are divided into α-thalassemia and β-thalassemia. Pathogenic deletions cause the β-thalassemia in the β-globin, which includes several genes, whereas the β-thalassemia usually results in specific point mutations in the β-globin genes that result in the decrease or abnormal production of the different β-globin subunits (Table 2) (18). The individuals with heterozygous mutation (carriers) are referred to as β-thalassemia minors, resulting in milder hemolytic anemia. Simultaneously, the homozygous affected individuals suffer a more severe form of the disease (β-thalassemia major) (18). It has also been observed that the patients suffering from β-thalassemia might also inherit the SCD gene (HbS b-thalassemia), which mostly results in a variable phenotypic appearance and expression depending on the average Hgb production (18).

Several genes have been reported in the literature causing hemoglobinopathy-related phenotypes such as *HBB* (OMIM 141900), *HBA1* (OMIM 141800), *HBA2* (OMIM 141850), *HBG1* (OMIM 142200), *LCRB* (OMIM 152424), *HBD* (OMIM 142000), and *HBG2* (OMIM 142250).

Haemoglobinopathy Burden

Specific registries and screening programs for hemoglobinopathies serve a great deal in properly outlining such disorders' current status in establishing standard preventive strategies, treatment protocols, and managing updated health system policies. These registries and programs play a key role in formulating and recommendations of standard guidelines and measures to enhance the diagnosis, patient care, and prevention national wide (19).

Preventive Measures

As there is no radical cure for the vast majority of affected individuals suffering from this severe disorder, preventive measures to restrict such affected children's birth are necessary for hemoglobinopathies. Using the latest

Table 2. *Classifications of α-thalassemia and β-thalassemia.*

Type of thalassemia	Description
α-Thalassemias	
Deletion of 1 α-globulin gene: silent carrier state	Hb size normal or slightly reduced and asymptomatic clinically
Deletion of 2 α-globulin gene: mild α-thalassemia	Microcytic hypochromic anemia (mild), affected individuals suffer from light-headedness and fatigue
Deletion of 3 α-globulin gene: HbH disease	Microcytic hypochromic anemia (Mild) or HbH disease, the affected individual may require blood transfusions
Deletion of 4 α-globulin gene: Bart's Hb	The affected individual may not survive
β-thalassemias	
Carrier (heterozygous): minor	Clinically asymptomatic
Moderate impairment to one or both alleles: intermediata	If symptomatic, the affected individual requires blood transfusions
Both alleles mutated (homozygous): major (Cooley's anemia)	Hypochromic microcytic anemia (severe), and needs blood transfusions throughout life

technologies such as next-generation sequencing, proper diagnosis at the molecular level, identification of carriers (heterozygous), proper genetic counseling, prenatal testing, or pre-implantation genetic diagnosis are the key elements to eradicate this disorder. These strategies should be implemented in countries having a high risk of such disorders due to breeding within families and lack of modern genetic and diagnostic technologies (19).

Saudi Arabia Concerns

As far as Saudi Arabia is concerned, the main hurdles in the success of the PMSGC include (a) non-cancellable wedding plans, marriages within families (43%), (b) social stigma fear and following cultural norms (21%), (c) familial pressures and upholding family commitment (17%), and (d) religious contemplations (14%) (20).

It has also been observed that late screening at the time of marriage is also a significant issue. Thus, it is a significant barrier, as, at that time, wedding plans cannot be canceled. In such situations, premarital screening is a late choice for couples who had already committed to their marriage. Thus, this sociocultural stigma and pressure are among the main reason for the prevalence of these disorders in Saudi Arabia and other Muslim countries (21). Along with some religious norms of acceptance of fate and accepting the risk of a sick child, some other major reasons include fear of society, publically declaring carrier status of individuals, lack of knowledge, and education regarding hereditary diseases (8).

However, genetic counselors' inability to provide sufficient information regarding the disease risk and considering termination illegal is also considered a key barrier (8,22).

Population-Based Prenatal Screening

Saudi Arabia was the first Muslim country to introduce preimplantation genetic diagnosis, accepted by the Islamic religion. Using this approach, the fetus having the disease phenotype may be terminated (23). However, the process is very complicated, expensive and requires an expert team, which may be implemented to screen the hemoglobinopathy in future in this part of the world (5,24).

Population prenatal screening should be implemented in the Kingdom of Saudi Arabia for different common disorders. The screening program should include every healthy newborn, which will help to identify carriers and couples that may give birth to an affected child. The primary screening steps include full blood count, biochemical analysis (quantitative high-Performance liquid chromatography analysis, or capillary electrophoresis). Structural Hb variants (mainly, SCD) could be identified using tandem mass spectrometry. However, next-generation technology is available in different research institutes and universities. This is the time to implement fast, accurate molecular diagnosis using these state-of-the-art facilities (22,24,25).

Genetic Counseling

After successful genetic and molecular testing, the mutation in a specific gene responsible for the disorder is identified. Thus, the couples and individuals are counseled by their physician regarding the disease severity, risk, and carrier status. These tests should be implemented for all the newborns in the country. In Muslim countries, it is socially and religiously unacceptable to bear a child without marriage. Thus, β-thalassemia carriers can be identified before marriage using molecular tests (26).

Therapeutic Advances

The use of proper management and monitoring of the affected individual having hemoglobinopathies increased the patients' life expectancy. These therapeutic advances have also improved the patients' treatments

in terms of oral iron chelation, such as advances in the combined chelation regimens and early iron overload detection (27,28). It has been observed that affected individuals survive up to 55 years (average one quarter), whereas 61-year-old patients having different types of hemoglobinopathy have also been monitored. Hence, 25 years of data from Italy having 977 registered patients suffering from TM suggested that 68% of patients were alive at the age of 35 (29).

Iron Overload

Iron overload is a significant issue and a cause of mortality and morbidity resulting from excessive iron absorption in the intestine or during transfusion in patients suffering from thalassemia intermedia (TI) and thalassemia major (TM). This overload may advance with age and might affect several key organs such as the liver, heart, other severe complications, or even death. Iron overload is traditionally detected using the serum ferritin levels; however, many patients might have normal serum ferritin levels and still have the disorder. Magnetic resonance imaging (MRI) using the T2* sequence has also been used to detect and diagnose evaluate liver and myocardial iron concentration (30). Heart MRI might help to understand the heart complications and support the clinicians to make therapeutic strategies or educate the patient regarding the disease (31). An early initiation of chelation therapy and close and regular monitoring are the basic mechanisms in preventing or reducing the iron overload mechanism.

Microbial Infections

Patients having SCD and thalassemia mostly die due to severe microbial infections (32,33). The death rate can be reduced if the infection is identified early and managed adequately (34). The main factors notable under these infectious circumstances include iron overload, splenectomy, severe anemia, advanced age, gallstones, and facial deformities (34-36). It has been reported that microbial infection of Gram-negative microorganisms may result in spleen damage that might result in splenectomy (37,38).

Premarital/Preconception Period

The couples who wish to marry must be subjected to genetic screening and counseling in all the government and non-government facilities. Genetic counseling must be provided by trained clinicians, having expertise in molecular diagnosis that might advise future pregnancies and the risk factor involved (39,40).

Prenatal Period

Postnatal depression and therapeutic abortion should be implemented and reviewed according to legal obligations in different Muslim countries such as Iraqi Kurdistan, Bahrain, Iran, and Turkey authorizing legal abortion 16 weeks before the gestation period thalassemia patients/ fetuses (41).

Neonatal Period

Individuals born with this severe disorder require appropriate support and considerable care to live a safe and prolong life. Thus, couples with an affected child need both care, support, and adequate genetic counseling regarding the future pregnancies.

Covid-19 and Hemoglobinopathies

Individuals having COVID-19 infection revealed a normal CBC and lactate dehydrogenase on admission, and one of the infected patients revealed thrombocytopenia, which is a common finding in other viral illnesses such as dengue fever (42). However, the meta-analysis studies showed that in severe COVID-19 cases, Hb values are substantially reduced, confirming previous evidence garnered from patients with other pneumonia (43). A decline in the Hb concentration may result in severe clinical outcome for the patient. Thus, preliminary monitoring and evaluation of Hb values in patients with the COVID-19 should be considered a priority. The physicians caring for patients with any hemoglobinopathies should consider transfusion support. The interaction between Hb and COVID-19 would open a new window for future research endeavors (44).

Conclusion

In conclusion, the proper working of different types of registries in Saudi Arabia will help the government to estimate the total number of carrier individuals, their burden on society, current status, and sufferings. This will help the local regulating authorities step forward and build formulate effective policies, improve healthcare providers' working, increase public awareness regarding the disease and prenatal testing, and formulate standard prenatal testing and genetic counseling guidelines. These awareness programs will educate the local population and provide knowledge regarding the benefits of the screening programs. Furthermore, there is a need to collaborate among national and international organizations in terms of expertise and laying out standard plans to properly eradicate this severe disorder.

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Author details

Muhammad Umair[1], Majid Alfadhel[1,2]

1. Medical Genomics Research Department, King Abdullah International Medical Research Center (KAIMRC), King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia
2. Division of Genetics, Department of Pediatrics, King Abdullah Specialized Children's Hospital, King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Riyadh, Saudi Arabia

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