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Significance of premarital screening and genetic counselling program for hemoglobinopathies

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Abstract

Introduction: Premarital screening includes general medical examination by which the promotion of a woman's and her partner's health and well-being prior to conception. It is regarded as a primary preventive approach for couples planning to conceive, as well as an important step toward protecting society of disease's spread. Hemoglobinopathies are one of the most frequent autosomal recessive illnesses in Iraq, which may associate with significant mortality and morbidity. Its inherited disorders and run down through families. Humans are affected by this disorder, which can occur due to the presence of quantitative and, or qualitative irregularities in the globin chains. Hemoglobin (Hb)S, which causes sickle cell disease (SCD), Hb-C or Hb-D illness, and other qualitative abnormalities, is the most prevalent. α- and β-thalassemia are quantitative anomalies with reduced or missing production of β or α globin chains are the most common. The world's most common single-gene diseases, particularly in the Eastern Mediterranean region, which includes Iraq

Conclusion :All of the above data support the concept of a haemoglobinopathies prevention program based on premarital screening, counseling, and prenatal diagnosis with the aim of decrease the number of afflicted children born in the region

Keywords:

1.Introduction

Premarital screening is a procedure that couples go through before getting married to check for certain inherited, infectious, or blood-borne disorders that could be passed down to their children.(Hamali and Saboor, 2019). Premarital screening is now one of the most significant preventative strategies for genetic abnormalities, congenital defects, and a variation of medical and psychological marriage issues (Al Sulaiman *et al*. 2008). Premarital Counseling is the best option because it is widely accepted from a religious and ethnic standpoint, as well as having low health and financial implications (Rahman, and Islam, 2014). Consanguineous and additional types of relation marriages are encouraged in Iraq and other Muslim countries, which leads to a rise in the incidence of recessive genetic disorders

The presence of qualitative and, or quantitative anomalies affecting the globin chains defines haemoglobinopathies, which are among the most frequent autosomal recessive illnesses affecting humans. Hemoglobin (Hb)S, which causes sickle cell disease (SCD), Hb-C or Hb-D illness, and other qualitative abnormalities, is the most prevalent.

The most common quantitative abnormalities are α- and β-thalassemia, which are caused by reduced or missing production of the β and α globin chains, respectively. Thalassemia is the most common single-gene disease in the world, especially in the Eastern Mediterranean region, which includes Iraq (Hamamy and Al-Allawi, 2013) (Al -Allawi & Al-Dousky, 2010).

The third Royal Decree mandated sickle cell anemia and thalassemia premarital screening in (2004). After being checked for sickle cell anemia and thalassemia, a couple getting married must get a certificate from an authorized health center declaring their thalassemia and sickle cell anemia status. Another key objective of this program is to provide counseling to at-risk couples.

2. Hemoglobin

Hemoglobin molecules (Hb.) are tetramers made up of four polypeptide chains, each with a heme group attached. These polypeptides come in a variety of chemical forms. A distinct gene controls each chain, which is active and inactivated in a certain order. Two sets of genes (i.e. four genes) are found on chromosome No. 6 and govern the alpha chain. The Beta, Gamma, and Delta chains are each controlled by a single pair of genes (i.e. two genes) found on chromosome 11.(Gamal, 2013).

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The red cells should carry oxygen to the tissues and carbon dioxide from the tissues to the lungs for optimal gaseous exchanges. They should have a particular protein, hemoglobin, to perfume this gaseous exchange(Hall, 2010).

Normal adult hemoglobin A (Hb A), the main hemoglobin beyond the age of three–six months, is made up of 4 polypeptide chains, with haem group for each one. Hb F and Hb A2 are two more hemoglobins found in modest amounts in normal adult blood. These also have α chains, but instead of β chains, they have γ and δ chains, respectively(Hoffbrand and Steensma, 2019) (Table 1.1).

Switching from Hb.F to Hb.A is usually physiological but the mechanism is unclear. Hb.F α2 γ2 binds O_2 more tightly than adult hemoglobin, ensuring adequate O_2 delivery to the fetus which must extract its O_2 from mother's circulation. After birth the lungs expand and the O_2 is derived from the air, with β.chain production replacing that of γ chain , leading to an increase in adult hemoglobin α2 β2 (Provan *et al.*, 2015).

Table (1) Normal Haemoglobins Chain in Blood of Fetus and Adult

Hemoglobin	Amount	Globin chains
Fetus Hemoglobin		
Hb F	85%	α2 γ2
Hb A	5–10%	α2 β2
Adult Hemoglobin		
Hb F	0.5–0.8%	α2 γ2
Hb A	96–98%	α2 β2
Hb A2	0.5–3.2 %	α2 δ2

Hemoglobinopathies

The incidence of quantitative and or qualitative anomalies affecting the globin chains defines haemoglobinopathies, which are through the most frequent autosomal recessive illnesses affecting humans (Hamamy and Al-Allawi, 2013). Thalassemia is caused by quantitative errors, whereas qualitative variations, known as Hb variants, produce a variety of illnesses such as unstable Hb, sickle cell disease, increased oxygen affinity, decreased oxygen affinity, and methemoglobinemia (Hoffbrand *et al.*, 2016).

Classification of Hemoglobinopathies

Hemoglobinopathies are divided into two categories: thalassemia syndromes (α- and β thalassemia) and structural hemoglobin variations. Hemoglobin (Hb)S, which causes sickle cell disease, Hb-C or Hb-D disease, and others are the most common (Payandeh *et al.*, 2014).

Thalassemia syndromes

Thalassemia is a common and global human monogenic disease. It is a hereditary anemia caused by hemoglobin (Hb) gene clusters mutations that slow down the production of one or further of the globin chain subunits (Cappellini et al., 2018).

two types of thalassemia are presented: those in which a mutation affects the protein amount , and those in which a structural alteration in the hemoglobin molecule causes the generation of a variant protein (hemoglobinopathies). These include-and -thalassemia, in which the hemoglobin molecule's globin chain is insufficiently synthesized. β-thalassemia in the homozygous state is the clinically most dangerous disorder, and α thalassemia homozygotes are frequently deadly in utero. The genes of thalassemia are found all over the world, from the Mediterranean basin and Sub-Saharan Africa to the Middle East, including South China and the Pacific Islands. These genes are rare in indigenous people in northern regions, but they have spread due to population movements (Taher and Cappellini, 2018).

Classification of thalassemia

The thalassemia syndromes are usually classed as α-thalassemia and β-thalassemia depending on the causal genetic abnormality, while according to clinical severity classify to thalassemia major, thalassemia intermediate and thalassemia minor (Lee *et al.*, 2019).

Structural Variants of Hemoglobin

Hemoglobin's structural variants are caused by a single amino acid substitution in the chain of globin caused by a point mutation in the gene globin.

Hemoglobin (Hb) structural variants are usually caused by a single amino acid substitution in the globin chain caused by a point mutation in the globin gene. Although the majority of these polymorphisms are of minor clinical importance, a few key subgroups have been discovered. Sickle cell anemia is caused by homozygous Hb S, whereas Hb E and Hb D homozygotes are only weakly affected (Clarke and Higgins, 2000).

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α-Thalassemia

In alpha thalassemia, the alpha protein is not produced enough by hemoglobin. Four genes are needed, two of them from each parent, in order to produce alpha-globin protein chains. If 1of the 4 genes or more is missing, the results will be alpha thalassemia. The α-thalassemia genotypes, syndromes and clinical features are shown in table (1-2) (Farashi and Harteveld, 2018). The severity of thalassemia is determined by the number of defective thalassemia genes.

when:

- One faulty gene: it is also known as alpha thalassemia minima. The patient is asymptomatic. A carrier is a healthy person who has a child with thalassemia symptoms.
- Two faulty genes: minor alpha thalassemia, where the patient has mild anemia.
- Three faulty genes: a chronic anemia, the patient has hemoglobin H disease. a regular blood transfusion will be needed throughout the patient's life (Lee *et al.*, 2019).
- Four faulty genes: The common severe form of alpha thalassemia is alpha thalassemia major. Hydrops fetalis (Bart's) is a dangerous disorder in which fluid accumulates in various regions of the fetus' body. Even with blood transfusions, a fetus with four mutant genes cannot manufacture normal hemoglobin and is unlikely to live(Jatavan *et al.*,2018).

Table (2) α-Thalassemia genotypes, syndromes and clinical features.

α-Thalassemia	α-Gene	Globin's Chain	Hemoglobin	Clinical features
Normal	αα / αα	$\alpha_2 \beta_2$	A	Normal
Silent carriers	αα / α -	$\alpha_2 \beta_2$	A	Asymptomatic
Trait (minor)	α - / α - - - / αα	$\alpha_2 \beta_2$	A	Asymptomatic
Hb H disease	- - / - α	α2 β2, β4	A, H	Jaundice, splenomegaly, occasionally need transfusion
Hydrops Fetalis	- - / - -	γ4, ξ2γ2	Barts Portlan	Lethal, Death in utero or shortly after birth

β-Thalassemia

2 globin genes, 1from each parent, are required to create beta-globin chains in β -thalassemia. Beta thalassemia develops when one or both genes are defective. The severity is determined by the number of mutant genes, β-Thalassemia genotypes, syndromes and clinical features are shown in table (1-3) (Thein, 2018).

- One faulty gene: it is known as minor beta thalassemia (Heterozygosity).
- Two faulty genes: major thalassemia (Homozygosity), and used to be called Cooley's anemia. It shows moderate or severe symptoms.

People of Mediterranean heritage are more likely to have β - thalassemia. West Asia, North Africa, and the Maldives Islands have greater rates of infection (Thein, 2018).

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Table (1.3) β-Thalassemia genotypes, syndromes and clinical features.

β-Thalassemia	β-Gene	Globin's Chain	Hemoglobin	Clinical features
Normal	β/ β	α 2 β2	A	Normal
Thalassemia minor (Trait)	β + / β β 0 / β	α 2 β2, α 2 δ 2 α 2 γ2	A, A2, F	Asymptomatic
Thalassemia Intermediate	β + / β0 β + / β+	α 2 β2, α 2 δ 2, α 2 γ 2	A, F	clinical phenotype between thalassemia trait and thalassemia major
Thalassemia Major	β + / β + β 0 / β 0	α 2 β2, α 2 δ 2, α 2 γ 2 α 2 δ 2, α 2 γ 2	A, A2, F F, A2	Require chronic transfusion; iron overload in endocrine abnormalities and chronic organ damageα

Homozygous Hb S

The term "sickle-cell disease" is a group of hemoglobinopathies marked by intravascular hemolysis and impaired oxygen delivery. Adult hemoglobin (Hb A) is formed when 2 globin subunits, 2 globin subunits, and a central heme molecule join in a typical red blood cell (Elagouz *et al.*, 2010).

Hemoglobin S (Hb S) resulting by a single amino acid substitution at the sixth position in the -globin chain, where a valine replaces a glutamic acid. A glutamic acid to lysine mutation in the -globin molecule causes hemoglobin C (Hb C).(Schachat *et al.*, 2017). Red blood cells with SCD have a tendency to deform and become sickle-shaped (like a crescent moon) rather than their regular disc shape, this can result in a variety of issues (Switzer *et al.*, 2006). Hb S molecules that have been deoxygenated form liquid crystals (tactoids) that deform erythrocytes into stiff sickle forms. (Jenerette and Brewer, 2010)

Hb E

Hemoglobin E is a physically defective hemoglobin caused by an amino acid substitution at the number 26 amino acid of beta globin (lysine for glutamine). (Avery, 2005). This results in decreased -E chain synthesis and a thalassaemia phenotype. (Thachil, Owusu-Ofori and Bates, 2014). The Hb E trait is analogous to a minor form of -thalassemia. Microcytosis is more common in homozygotes, yet they are still asymptomatic. (Chapin and Giardina, 2018). Multiple heterozygotes for β thalassemia and Hb E usually have a milder illness and produce varying of Hb A, with the mildest phenotypes caused by from mild β type mutations like 28 (A → G) and codon 19 (G → A), though some patients with severe β +-type mutations like IVS I-5 (G → C) and IVS II-654 (C → T) can produce symptoms as severe as Hb E/0-thalassemia (Old, 2013).

Hb D

The other common defective hemoglobin D is resulting from a mutation in the-or -chain genes (Frenette and Atweh, 2007). The -globin chain or the -globin chain are both involved in Hb D. Glutamate is swapped for lysine at the 121st position in the-globin chain variant, while asparagine is replaced by lysine at the 68th position in the -globin chain version, also known as Hb G Philadelphia (Refaldi, Mocellin and Cappellini, 2007). Mild hemolysis occurs in the homozygous state, with few, if any, symptoms. Sickle cell disease is caused by the co-inheritance of both of these mutations with Hb.S (Rees and Arya, 2014).

Conclusions

Hemoglobinopathies are one of common inherited disorders in our country and its of many types depending on underlying genetic defect and it run within family. This supports the idea of implementing a haemoglobinopathies prevention program based on the concepts of counseling, premarital screening, and prenatal diagnosis in order to reduce the number of affected children born in our nation.

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