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RESEARCH PAPER

Proposed low-cost premarital screening program for prevention of sickle cell and thalassemia in Yemen

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ABSTRACT

In Yemen, the prevalence of sickle cell trait and β-thalassemia trait are high. The aim of this premarital program is to identify sickle cell and thalassemia carrier couples in Yemen before completing marriages proposal, in order to prevent affected birth. This can be achieved by applying a low-cost premarital screening program using simple blood tests compatible with the limited health resources of the country. If microcytosis or positive sickle cell is found in both or one partner has microcytosis and the other has positive sickle cell, so their children at high risk of having sickle cell or/and thalassemia diseases. Carrier couples will be referred to genetic counseling. The outcomes of this preventive program are predicted to decrease the incidence of affected birth and reduce the health burden of these disorders. The success of this program also requires governmental, educational and religious supports.

INTRODUCTION

Premarital screening and genetic counseling (PMSGC) programs for prevention of blood genetic diseases have been implemented in many populations with high prevalence rates of inherited blood disorders worldwide since the 1970s.[1,2] They aim to identify hemoglobinopathies carriers, in order to evaluate the risk of having children with severe anemia. Sickle cell disorder (SCD) and thalassemia are the most common hemoglobin (Hb) gene diseases in the world forming an important public heath problem in certain regions of the world including the Mediterranean and Middle East countries.[3]

SCD and thalassemia are autosomal recessive inherited Hb disorders. SCD is a group of Hb disorders

resulting from the inheritance of the sickle β-globin gene. The clinical manifestations of SCD are due to the tendency for Hb S variant to polymerize and deform red cells into the sickle shape under deoxygenated conditions. The homozygous sickle cell anemia (Hb SS) is the most common severe type of SCD. Thalassemias are a heterogeneous group of inherited disorders of globin synthesis that lead to a reduction of one or more of the globin chains. This unbalanced production of globin chain results in a decrease in Hb synthesis and microcytosis and hypochromia. The homozygous β-thalassemia is the most common severe form of thalassemias. The compound heterozygous sickle cell/β thalassemia also causes a severe anemia which is common in populations with high prevalence rates of both SCD and β-thalassemia.[4]

The available treatment for sickle cell and thalassemia diseases are unsatisfactory and usually the patients depend on blood lifelong transfusion for survival, which causes a considerable stress for patients and their relatives; in addition to economical and emotional burdens on the society and the health system. Premarital screening is the best option for reducing Hb gene disorders than prenatal screening because the first is primary prevention whereas the latter is secondary or tertiary prevention.[5] Premarital screening for thalassemia was first established in 1975 in Latium, Italy[2] whereas for SCD in Virginia, USA in 1970.[1] They are currently carrying out with proven success in many parts of the world including the Mediterranean countries such as Greece, Italy and Cyprus with success preventive of 80-100%. In Arab countries like Egypt, Syria, Lebanon, Tunisia, Morocco, Saudi Arabia, Bahrain and United Arab Emirates and other developing countries, the success rates of these programs were satisfactory due to the economical obstacles or other heath priorities (infectious disease) or cultural and religious constraints.[6]

Strategies of implementing premarital preventive programs in high-risk populations vary according to the economic status, culture and religion of these populations. In developed countries where advanced technologies are available advances in carrier diagnosis using hematological examination followed by DNA investigation has made population possible screening and prenatal diagnosis during pregnancy. This approach, in conjunction with genetic counseling, has lead to a steady decrease in the birth of affected homozygote in those countries, and raised the knowledge of the risk of being a carrier. However, the premarital preventive program has been introduced into many developing countries by using simple and inexpensive blood tests in combination with genetic counseling and has resulted in a noticeable reduction in the number of affected birth. For example in Saudi Arabia, complete blood count (CBC), sickle cell test and Hb-electrophoresis were used in the premarital screening leading to more than 70% reduction of the prevalence of β-thalassemia during the period of 2004 to 2009.[7]

BACKGROUND

Yemen is a poor country with a population of 24 million[8] and limited health resources. The prevalence of sickle cell trait (Hb AS) in Yemen is 2.2%, with a higher frequency in the western coastal and mid-western parts of the country where the incidence of affected homozygous births (Hb SS) may reach up 20/10,000.[9] Also the prevalence of β-thalassemia trait is 4.4%[10] with an estimated incidence of 11.3/10,000 of homozygous β-thalassemia births in the western coastal and mountainous regions of Yemen. The prevalence of thalassemia in SCD found to be high (19.4%) in Taiz region in mid-western area of the country.[11] The incidences of affected birth of either homozygous sickle cell anemia or β-thalassemia could be higher, depending on the proportion of consanguineous marriages and the frequency of heterozygous Hb S/β-thalassemia disease.

The most effective factor for high prevalence and incidence of sickle cell and β-thalassemia diseases in Yemen is the consanguineous marriages, which was reported to be high (44.7%) and traditional.[12] To reduce the number of affected birth and their social, emotional and economical burden on the family and health system in Yemen, it is essential to apply PMSCG program. There is no any premarital screening preventive practice in Yemen yet. Therefore, this simple and low-cost premarital screening program is proposed to be suitable for the limited health resources of the country. Such proposal is essential to evaluate how a premarital screening program can be implemented in Yemen.

DESIGN OF PREMARITAL SCREENING PROGRAM:

Preventing sickle cell and thalassemia diseases at high-risk population by carrier screening and genetic

counseling is proved to be an acceptable and effective process to reduce the number of affected birth.[6,13,14,15] This program consists of premarital screening and genetic counseling that is designed to produce a general infrastructure for accessible prevention of SCD and thalassemia before completing marriages proposal. Screening programs with genetic counseling can be implemented initially at high-risk populations in local communities in different parts of Yemen. To begin with, optional premarital screening using inexpensive and simple blood tests. Only couples at risk will receive information and genetic counseling about the consequences effects on the health of their children.

Relevant instruments, methods, trained health workers, target groups and genetic counseling are required to carry out this preventive program. Hematological analyzer machines are required for CBC analysis to determine the microcytosis and/or hypochromia in red blood cells. Methods of sickle cell using either sickling test or solubility test also are required for detection of Hb S. Genetic counselors consist of trained doctors or professionals with Bachelor of Science degrees in health studies that will provide advices to carrier couples about the genetic condition, which may affect them, so that the couples have to make the appropriate choices concerning marriage and reproduction. Target groups in the country are required to be prepared for premarital screening which can be preformed by giving classes about SCD and thalassemia for young people in high schools, universities, sports clubs and military. In addition, the widespread of education programs through booklets, posters, TV and newspapers. Public and private laboratories equipped and licensed to screen for SCD and thalassemia can be the place for premarital screening. Carriers' data will be recorded for evaluation to adapt this preventive program to meet the public needs.

PROCESS OF SCREENING

All prospective couples have to be tested for both diseases and get the appropriate counseling (if needed) before completing their marriage proposals. Therefore, couples with marriage proposals will be referred to a local licensed equipped laboratory for premarital screening. After filling the premarital form (name, age, sex, national number, and address), the man's CBC and sickle cell test are tested first, because of high prevalence of iron deficiency among women of

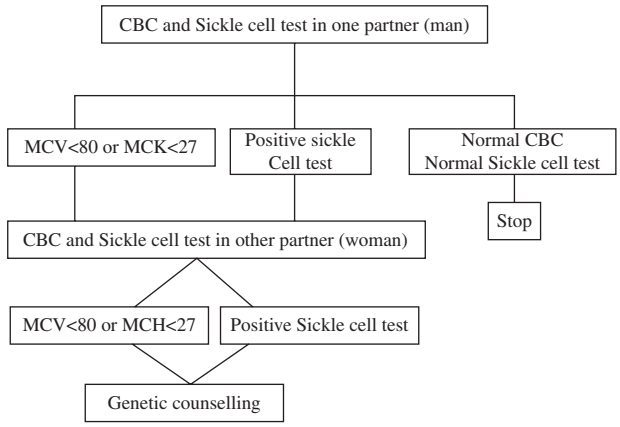

Figure 1. Premarital screening program for thalassemia and sickle cell disease.

reproductive age,[16] which also causes microcytosis. If he has microcytosis [mean cell volume (MCV) < 80% and/or mean cell Hb (MCH) < 27 pg] and/or positive sickle cell test, then the woman is examined. If microcytosis or positive sickle cell test is found in both or one partner has microcytosis and the other has positive sickle cell test, so their children are at high risk of having sickle cell and/or thalassemia diseases (Figure 1). The carrier couples will be referred to genetic counseling regardless to the results the couples has the choices concerning marriage and reproduction.

INTERPRETATION PROBLEMS

Because the common causes of microcytosis are thalassemia including α- and β-thalassemia trait, and iron deficiency anemia, the important problems encountered are the interpretation of

1. Microcytosis due to β-thalassemia trait or non β-thalassemia

The identification of β-thalassemia trait is very important because homozygous or compound heterozygous traits with sickle cell causes severe anemia; however, cases of α-thalassemia are very rare. A definitive diagnosis of β-thalassemia trait is based on microcytosis and high level of Hb A_2 > 3.5%. In very low health resources situations such as in Yemen where sophisticated equipments for measuring Hb A_2 level often unavailable, the β-thalassemia trait can be predicted by introducing one of well-known mathematical formulae as simple, fast and inexpensive method of discrimination between β-thalassemia trait and other causes of microcytosis and hypochromia. Some of these formulae have been applied in similar circumstances like in some health centers in Isfahan,

Table 1. Definition of formulas.

Index	Formula	β-thalassemia trait	Non- β-thalassemic
England & Fraser[19]	MCV-RBC-5Hb − 3.4	<0	> 0
Mentzer[20]	MCV/RBC count	<13	>13
Shine and Lal[21]	MCV^2 × MCH/100	<1530	>1530

Iran, as part of the premarital screening program.[17] The diagnosis of these formulae is based on red cell indices obtained by hematological analyzer analysis (Table 1). Although none of these formulae are absolutely accurate, but they can recognize β-thalassemia trait from iron deficiency and α-thalassemia with limitations. Each one of these formulae showed different sensitivity and specificity in different populations. For example, England and Fraser index showed sensitivity >95% and specificity >95% among a population from Kuwait,[18] whereas a sensitivity of 87.2% and specificity of 62.9% among people from Iran.[17] In the meanwhile, any one of these formulae can be used in this proposed program, until their sensitivity and specificity among Yemeni population are determined.

2. Microcytosis due to coexisting of iron deficiency anemia and β-thalassemia trait

Iron deficiency anemia is common among women of reproductive age.[16] This can be evaluated by rechecking their red cell indices after iron therapy for six weeks to clarify persistent microcytosis that may be due to β-thalassemia trait.[22]

EXPECTED OUTCOMES

The success of this proposed premarital screening program depends on the health resources, governmental policies, religious beliefs, culture norms, traditions, literacy and education level and attitudes of individual couples. It is predicated that this premarital preventive program may be accepted with some difficulties because of its economical viability, accessibility within local health services and couples want a healthy family. The difficulties of accepting this program may be due to marriages among the same family or tribe are traditional; in addition to religious reasons, however, the number of affected birth will be decreased which would reduce the health burden on the individuals and society. They will also provide the research scientific data about SCD and thalassemia which promoting further development of genetic knowledge and technology that will lead to improve premarital preventive program.

Disadvantage of using mathematical formulae for discrimination β-thalassemia trait from α-thalassemia or iron deficiency anemia in this proposed preventive program will miss some cases, which will lower the reducing number of affected birth. This will be a major problem until advanced technology is established.

FUTURE ASPECTS

Development of genetic preventive services will be in response to public demand. Future planning should be taken after evaluating the outcomes of implementation of this preventive program taking into account the introduction of advanced technology such as Hb-electrophoresis or high performance liquid chromatography (HPLC) into the local health services to determine the levels of Hb A_2, F and S and other abnormal Hb for accurate diagnosis of β-thalassemia trait, sickle cell trait and other hemoglobinopathies carries. In addition, the establishment DNA techniques to confirm the primary screening results and to study the nature of the mutations involved for predicting the likely severity of the disorders resulting from their inheritance should be considered.

Governmental legalization for mandatory premarital screening may be applied at high risk population with genetic Hb disorders or nationally (if necessary) to reduce as much as possible the number of affected births with these diseases. Prenatal diagnosis services may also be introduced into the health services with legalization for termination pregnancy of affected fetuses.

Premarital preventive program can also be extended to screen for viral infections particularly human immunodeficiency (HIV) and hepatitis viruses B and C (HBV, and HCV) because of their high prevalence rates and capability for sexually transmission and their serious clinical consequences.

CONCLUSION

Premarital screening and genetic counseling program using simple and inexpensive blood tests, initially for preventing sickle cell and thalassemia diseases can be introduced at high-risk population in the western regions of Yemen. By applying this proposed preventive program it is expected to decrease the number of affected births which leads to reduce the health burden of these diseases for the benefits of the Yemeni people. In the future, it may be applied nationally and extended to include screening for infections and other genetic diseases. The success of this preventive program needs governmental, educational and religious supports.

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