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Prenatal Diagnosis and Frequency Determination of alpha and beta Thalassemia, S, D, C, and H Hemoglobinopathies; Globin Mutational Genes Aanalysis among Voluntary Couples from Ahvaz

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Abstract

Background: The aim of this perspective study was to assess the frequency of hemoglobinopathy mutational genes among voluntary hemoglobinopathy carrier couples-to-be referred to thalassemia center, Shafa hospital, affiliated to Ahvaz Jondidishapur University of Medical Sciences (AJUOMS), during their first trimester of pregnancy for genetic screening and counseling for prenatal diagnosis (PND).

Materials and Methods: In a four-year period (2000-2004), 93 voluntary couples from Khuzestan province (mostly Ahvaz area) who were proved to be carrier for alpha thalassemia, beta thalassemia, or other hemoglobinapathies underwent PND and detection of causative mutational genes by chorionic villus sampling {CVS) plus direct or indirect DNA analysis at first trimester of pregnancy. First trimester authorized termination of pregnancy was performed, if a fetus was confirmed to have serious disorders.

Results: From 93 voluntary couples who underwent PND, 11 (10.3%) couples were confirmed to have fetuses with serious disorders, and interruption of pregnancy was performed for them. Prenatal screening and PND in this study showed that β-thalassemia was the most frequent accounting for 55% of all disorders. Results of other hemoglobinopathy mutational genes analysis showed the frequency of S, D, C, and α–globin mutational gene to be 16.2%, 3.2 %, 1%, and 9.7 %, respectively. Eighteen percent of cases were undetermined. Our data showed that the frequency of sickle cell mutational gene is second to β-thalassemia, α-thalassemia is the third one.

Conclusion: It is too clear that prenatal screening and PND is a useful keys methods for identifying the affected fetuses , expensive methods and the Ahvaz is on long distance far from the capital town (Tehran), only the rich voluntary family with high income accepted .this pathway solution. Recently Since 2007 these facility were set up in to Ahvaz Thalassemia center by co- ordination of Ministry of public health services through Iran national thalassemia screening program. Part-affiliated to(AJUOMS). Furthermore, the frequency of 18% others of unknown genetic traits still dictates further detailed studies that can elucidate the other types of genetic abnormities that exist in region.

Keywords: Prenatal screening, Prenatal diagnosis, Thalassemia, Hemoglobinopathy.

Introduction

Iran is a country with an area of 1,648,000 km^2 in the eastern Mediterranean region. The same as other neighboring nations in the region, Iran has a large number of major thalassemia patients. Its frequency varies considerably from area to area countrywide.[1,2] The highest frequency is observed around the Caspian Sea (more than 10%), and moderate frequency in Isfahan a city in the central part of Iran (4-5%). The frequency is about 8% in Fars province, south of Iran. Around Persian Gulf, the gene frequency is high and reaches 8-10%.[2,3,4]

There are numerous mutational genes responsible for beta thalassemia in the region. These mutations are mainly Iranian, Mediterranean, Kurdish, Egyptian, Tunisian, Indian, Asian–Indian, Chinese, and Afro-American in origin.[3,4] In Khuzestan province and other northern areas of Persian Gulf, sickle cell disease and other hemoglobinopathies are also present.

Materials and Methods

This study was done as a prospective study in a four-year period (2000-2004) in 93 voluntary couples from Khuzestan province (mostly Ahvaz city), who were proved to be carriers for alpha thalassemia, beta thalassemia, or other hemoglobinapathies. Fetal sampling was performed at first trimester of pregnancy at weeks 10-11 of gestational age. Chorionic villus sampling (CVS) was performed under ultrasonography guidance. If direct or indirect DNA analysis methods revealed serious disorders, authorized termination of pregnancy was performed in the first trimester. The collected data were reviewed and analyzed.

Results

From 93 voluntary couples who underwent PND, 11 (10.3%) couples were confirmed to have fetuses with serious disorders, and interruption of pregnancy was performed for them. Four were at risk of beta thalassemia major, 2 were at risk of sickle-thalassemia, 2 were at risk of sickle–hemoglobin (Hb) D, 1 was at risk for sickle hemoglobin C, 1 was at risk of sickle cell syndrome, and 1 was at risk of hemoglobin-H disease (table 1). Prenatal screening and PND in this study showed that β-thalassemia was the most frequent disorder accounting for 53% of all. Results of other hemoglobinopathy mutational genes analysis showed the frequency of S, D, C, and α–globin mutational gene to be 16.2%, 3.2 %, 1%, and 9.7 %, respectively. Eighteen percent of cases were undetermined (tables 2 and 3). Our data showed that the frequency of sickle cell mutational gene is second to β-thalassemia, α-thalassemia is the third one. Double homozygotes such as sickle-β thalassemia, sickle-hemoglobin D, sickle hemoglobin C, and sickle cell disease also present among affected fetuses.

***Table 1**. PND affected fetuses in the 93 CVS samples*

Affected fetus	No.
β-thalassemia	4
Sickle-thalassemia	2
Sickle-HbD	2
Sickle-HbC	1
HbH	1
Sickle cell disease	1
Total	11

***Table 2.** Total screening and parental α, β globin gene mutational analysis.*

Mutation	No. (%)
HbS	30 (16.2)
IVSII-I	29 (15.2)
3.7a	17 (9.1)
Fr 8/9	15 (8)
Fr 36/37	15 (8)
IVI-110	13 (6.9)
CD8	6 (3.2)
HbD	6 (3.2)
IVSI-II	3 (1.6)
IVSI-25	3 (1.6)
IVSI-30	3 (1.6)
HbC	2 (1)
C39	2 (1)
C5	2 (1)
Med-αα	1 (0.6)
Undetermined	35 (18)
Total	186

***Table 3.** PND and α, β globin gene mutational analysis from 93 CVS samples.*

Diagnosis	Mutations No. (%)
β-thalassemia	94 (53)
Sickle cell disease	30 (16)
α-thalassemia	18 (9)
HbD	6 (3)
HbC	2 (1)
Undetermined	36 (18)
Total	186

Discussion

In general terms**,** hemoglobinopthies are autosomal recessive disorders. Heterozygote cases are symptom-free but present hematological characteristics,[5,6] which are often useful for identification of homozygotes. The homozygote or genetic compound states result in clinically

significant phenotypes of variable severity including thalassemia major, thalassemia intermediate, sickle cell syndromes, hemoglobin H disease, etc. Carrier testing (screening) is to identify carriers of hemoglobin disorders in order to assess the risk of a couple having a severely affected child and to provide information on the options available to avoid such an eventuality. The risk of having affected children can be evaluated by blood tests before marriage or pregnancy, then PND can be performed by CVS at first trimester of pregnancy (10–11 weeks of gestational age).[6] Premarital screen is available in Iran (Khuzestan province), through national screening program for prevention of thalassemia. It was implemented in 1997;[7] couples planning to marry routinely attend district health centers for premarital education, family planning, and performing several blood tests.[7] In Khuzestan, prospective couples, who were both carriers were referred to Ahvaz Thalassemia Center affiliated to Ahvaz Jondidishapur University of Medical Sciences (AJUOMS) to one of the authors for counseling in the years of conducting this study. The program was conducted according to ethical principles.[1] To date no comparative study on alpha thalassemia, beta thalassemia, and other hemoglobinopathy mutations was carried out in Khuzestan province.[8,9] Our study showed that 10.3% of carriers had affected fetuses. The findings of mutational genes analysis revealed that homozygote β-thalassemia major is the most frequent mutational gene. All above genes are related to the β-globin genes on chromosomal 11, (except α-thalassemia on chromosome 16).[9] All of them are chronic hemolytic anemia with huge hepatosplenomegaly, many patients are on monthly regular blood transfusion. They are also accompanied with chronic infection. Patients are at risk for iron overload, endocrine, liver, and heart problems.[1,3]

Conclusion

Since 2007 PND facilities are implemented in Ahvaz Thalassemia Center by Ministry of Health and Medical Education through Iran National Thalassemia Screening Program, partly affiliated by AJUOMS. The 18% frequency of unknown genetic traits still dictates further detailed studies to elucidate other types of genetic abnormities that exist in the region.

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