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Carrier Screening and Prenatal Diagnosis of Hemoglobinopathies. A Study of Indigenous and Immigrant Couples in Northern Greece, Over the Last 5 Years

Stamatia Theodoridou [a]; Michael Alemayehou [a]; Nikolaos Prappas [b]; Olga Karakasidou [a]; Vasiliki Aletra [a]; Eleni Plata [c]; Panagiotis Tsaftaridis [c]; Photini Karababa [c]; Marina Boussiou [c]; Klio Sinopoulou [c]; Anna Hatzi [c]; Ersi Voskaridou [c]; Afroditi Loutradi [c]; Anna Manitsa [a]
[a] Haemoglobinopathy Prevention Unit, Hippokration Hospital, Thessaloniki, Greece [b] Fourth Department of Obstetrics and Gynaecology, Aristotelion University of Thessaloniki, Thessaloniki, Greece [c] Thalassaemia National Centre of Greece, Laikon General Hospital, Athens, Greece

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ORIGINAL ARTICLE

CARRIER SCREENING AND PRENATAL DIAGNOSIS OF HEMOGLOBINOPATHIES. A STUDY OF INDIGENOUS AND IMMIGRANT COUPLES IN NORTHERN GREECE, OVER THE LAST 5 YEARS

Stamatia Theodoridou,[1] Michael Alemayehou,[1] Nikolaos Prappas,[2] Olga Karakasidou,[1] Vasiliki Aletra,[1] Eleni Plata,[3] Panagiotis Tsaftaridis,[3] Photini Karababa,[3] Marina Boussiou,[3] Klio Sinopoulou,[3] Anna Hatzi,[3] Ersi Voskaridou,[3] Afroditi Loutradi,[3] and Anna Manitsa[1]

[1]*Haemoglobinopathy Prevention Unit, Hippokration Hospital, Thessaloniki, Greece*
[2]*Fourth Department of Obstetrics and Gynaecology, Aristotelion University of Thessaloniki, Thessaloniki, Greece*
[3]*Thalassaemia National Centre of Greece, Laikon General Hospital, Athens, Greece*

□ *Hemoglobinopathies constitute the most frequent monogenic disorders worldwide and thalassemias are the most frequent genetic disorders in Greece. Over a 5-year period (2002–2006), 1,375 couples were screened for hemoglobinopathies and counseled at our Thalassaemia Prevention Unit, Hippokration Hospital, Thessaloniki, Greece. In 148 cases (10.7%), both partners carried an abnormal hemoglobin (Hb) gene and genetic counseling was offered. One hundred out of 116 pregnancies were at-risk of giving birth to an offspring carrying either the homozygous or double heterozygous forms of the mutations under discussion. The remaining 16 pregnancies involved couples who were heterozygous for mutations that did not cause severe clinical disease, and were exempted from prenatal diagnosis. Twenty-six fetuses were found to be homozygotes or double heterozygotes for clinically significant mutations. These couples were informed of the danger of having an affected child but the termination or continuation of the pregnancy was left to the couples to decide. Nevertheless, all the couples preferred to terminate the pregnancies. The National Thalassaemia Prevention Programme has effectively decreased the incidence of thalassemia major and sickle cell syndromes in Greece.*

Keywords Thalassemia, Hemoglobinopathy, Gene mutations, Genetic counseling, Carrier screening, Prenatal diagnosis

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Address correspondence to Stamatia Theodoridou, M.D., Ph.D., Haemoglobinopathy Prevention Unit, Hippokration Hospital, Blood Bank Centre, Konstantinoupoleos 49, 54622 Thessaloniki, Greece; Tel./Fax: +30-31-2319782819; E-mail: hmesogiaki@ippokratio.gr

INTRODUCTION

Hemoglobinopathies constitute the most frequent monogenic disorders worldwide. They are due to mutations that affect the synthesis of the normal hemoglobin (Hb) chains or cause structural changes to the Hb molecule.

The thalassemias are the most frequent genetic disorders in Greece. β-Thalassemia (β-thal) carrier frequency is approximately 8%, while 1.5% of the population are carriers of the Hb S [β6(A3)Glu→Val] mutation. The rate of β-thal carriers could be as high as 15–20% in some areas (1). The risk of giving birth to a thalassemic child depends on the incidence of the thalassemic gene in the population under study. This may vary from 1/24 to 1/150 in married couples. It has been reported that Greece shares the same set of thalassemia mutations and a large number of rare defects similar to other Mediterranean countries (2). Currently, this incidence is influenced by the immigration to our country of people of Albanian and Southeast Asian origin (Kurds, Iranians, Iraqi, Pakistani and Philippines). In both areas, the thalassemia carrier rate and the incidence of various hemoglobinopathies are high. Currently, it is estimated that 10% of the population in Greece are immigrants, and of these, most (58%) are Albanians who have immigrated and settled in Greece in the last two decades (3).

Different investigators claim that DNA-based prenatal diagnosis was the most important contribution to thalassemia research in the three decades that followed the mid 1970s (4). Indeed, since the introduction of amniocentesis, chorionic villus sampling (CVS) and DNA analysis, thousands of couples have pregnancies without the fear of giving birth to thalassemic offspring.

The National Programme for Prevention of Thalassaemia was established in 1973. Through population screening and prenatal diagnosis programs that are performed by the National Centre for Thalassaemia in Athens (Greece) and the various Prevention Units throughout the country, ethnic Greeks and immigrants are screened and counseled free of charge. Carrier identification is not obligatory. Nevertheless, one of the main aims of the preventive program is that the whole population, and especially those at risk, are continually informed and made aware of the genetically inherited anemias that affect the Greek population, by implementing methods such as educational programs at schools, in the Armed Forces and through mass media. Maternity clinics also play a big role in directing pregnant women to the Thalassaemia Prevention Units for carrier identification. We report our findings on prenatal diagnosis of thalassemias and hemoglobinopathies in Northern Greece over a 5-year period (2002–2006).

MATERIALS AND METHODS

The hematological analyzer, Coulter ONYX (Beckman Coulter, Fullerton, CA, USA), was used to determine red cell indices (RBC, Hb, PCV, MCV, MCH, RDW). The VARIANT™ Hemoglobin Testing System (Bio-Rad Laboratories, Hercules, CA, USA), the β-Thalassemia Short program, an automated cation exchange high performance liquid chromatography (HPLC) instrument, was used for the quantification of Hbs A, F, A_2, S, C, and other variants. Hb A_2 levels were also quantified by column microchromatography (Helena BioSciences Europe, Gateshead, Tyne and Wear, UK). Alkaline pH and acid electrophoresis was carried out whenever abnormal Hbs were detected. Hb H inclusion bodies were identified by incubating the peripheral blood for 30 min. at 37°C with brilliant cresyl blue. Serum ferritin levels were measured by a micro-ELISA technique (Abbott Laboratories, Longford, County Westmeath, Ireland).

Individuals found to be heterozygous carriers were informed as to the nature of the genetic disorder, and they were also provided with an informative leaflet. Couples identified as being at-risk were also given genetic counseling and prenatal diagnosis was offered. The methods used for fetal sampling (i.e., CVS, amniocentesis and fetal blood sampling) were explained to the couple. Characterization of the type of mutation in the parents was carried out before or at the same time with fetal DNA analysis. Both DNA analysis and Hb biosynthesis were performed at the National Thalassaemia Centre, Laikon General Hospital, Athens, Greece.

RESULTS

During the 5-year period, a total of 21,372 subjects were screened individually or as couples at our Thalassaemia Prevention Unit at the Hippokration Hospital in Thessaloniki, Greece. We found that 9.9% were heterozygotes for β-thal, 3.8% for α-thal and 2.8% had Hb S [β6(A3) Glu→Val], Hb D-Punjab [β121(GH4)Glu→Gln], Hb O-Arab [β121(GH4) Glu→Lys] and Hb C [β6(A3)Glu→Lys] mutations.

There were 1,375 couples screened for hemoglobinopathies. This represents 6.5% of the total number of births in our hospital. Ninety-one percent of those screened were ethnic Greeks, while 9% were immigrants from the Balkans, Eastern Europe, Asia and Africa. In 811 couples (58.9%), both partners were not carriers of any abnormal Hb gene, while in 416 couples (30.2%), only one partner was heterozygous for thalassemia or another hemoglobinopathy. In 148 couples (10.7%), both partners carried an abnormal Hb gene and genetic counseling was offered. The proportion of at-risk pregnancies and the percentage of carriers in the population examined was found to be relatively high because our Thalassaemia Prevention