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RESEARCH ARTICLE

Five-year evaluation of premarital screening program for hemoglobinopathies in the province of Mersin, Turkey

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ABSTRACT

The prevalences of hemoglobin S (HbS) and β-thalassemia (β-thal) are high in Mersin, Turkey. In this study, the results of a five-year premarital screening program in Mersin province are reported. A total of 79,000 persons including 31,498 couples were screened in this program. Hematological analyses and electrophoresis were done to identify carriers. The results were given confidentially and at-risk couples were counselled on reproductive options and prenatal diagnosis. The carrier rates of hemoglobins (Hb) (HbS, HbD, HbE) and of β-thal were 1.21%, 0.17%, 0.04% and 2.04%, respectively. One hundred and thirty-four couples were at-risk, of whom 67.2% had health insurance. Twenty-seven couples did not become pregnant, six were divorced and 11 could not be reached. Of the 135 pregnancies, 80 had prenatal diagnosis. Five stillbirths occurred, and 18 homozygous babies were born to couples that did not seek prenatal diagnosis. Two families with prenatal diagnosis had affected babies: one was a late referral and the other due to religious reasons. For a successful screening program, emphasis must be on extensive and intensive informative programs for the public as a whole. Prenatal diagnosis should be offered free of charge as a basic public service. For a healthy population, knowledge and a shared responsibility between the public and the government are necessary.

Key words: Prenatal diagnosis, hemoglobin S (HbS), β-thalassemia, premarital screening

ÖZET

Mersin ilinde evlilik öncesi beş yıllık tarama sonuçlarının değerlendirilmesi

Mersin ilinde yüksek sıklıkta Hemoglobin S (HbS) ve β-talasemi saptanmıştır. Bu çalışmada Mersinde kurulan talasemi merkezinin 5 yıllık sonuçları verilmiştir. Toplam 79.000 kişi, 31.498 evlenecek çift taramaya başvurmuştur. Hematolojik analizler ve elektroforez ile taşıyıcılar saptanmıştır. Sonuçlar bireylere verilmiş, ve riskli çiftler doğum öncesi tanı ve üreme seçenekleri konusunda bilgilendirilmiştir. Hemoglobinlerden(Hb); HbS, HbD, HbE ve β-tal taşıyıcılığı sırasıyla %1.21, %0.17, %0.04 ve %2.04 olarak bulunmuştur. Toplam 134 riskli ailenin % 67.2'inin sağlık güvencesi vardır. Çiftlerden 6'sı ayrılmış, 11'inin adresi saptanamamış ve 27'inde gebelik yoktur. Toplam 135 gebelikten 80'i doğum öncesi tanıya gitmiştir. Tanı yaptırmayan riskli ailelerde 18 homozigot bebek doğmuştur. Ayrıca 5 ölü doğum olmuştur. Tanı konan iki aileden birisi geç başvuru diğeri dini nedenlerle hasta bebek doğurmuştur.

Sonuç olarak, başarılı bir tarama programı için halkın bu konuda tam bilinçlendirilmesi gereklidir. Ayrıca doğum öncesi tanı devlet güvencesine alınmalıdır. Sağlıklı bir toplum için bilgi ve halkla devletin sorumlulukları paylaşması gerekmektedir.

Anahtar sözcükler: Doğum öncesi tanı, Hemoglobin S(HbS), β-talasemi, evlilik öncesi tarama

INTRODUCTION

β-thalassemia (β-thal) and sickle cell anemia (SCA) are the most widespread single gene disorders in Cukurova, the lowland plains between the Taurus mountains and the Mediterranean Sea [1-11]. The first cases of SCA and β-thal from Mersin were reported by Aksoy in the 1950's and the high prevalence of both in Cukurova for the provinces of Hatay, Mersin and Adana has been reported by various authors since that time. The carrier rate for β-thal was found to vary from 0.1 to 10.3% and for hemoglobin S (HbS) from 0.1% to a high 44% in regions where the Arabic-speaking Eti-Turks are densely populated [1-11]. The rate of consanguinity is 30% [9,10]. Since there is no ultimate cure for these hereditary diseases, the World Health Organization (WHO) has suggested a control program comprising enlightenment of the public, screening for carriers, prenatal diagnosis and genetic counselling, which would result in the prevention of the birth of an affected child. Italy, Greece, Canada, the United Kingdom and Cyprus started the program in the 1970's and achieved success [12-19]. Though prenatal diagnosis has been available in Hacettepe University (1983), Bogazici University (1991) and Cukurova University (1992), the number of referrals has been few [20-23]. The Turkish Parliament passed a law for the prevention of these disorders in 1998 and the Ministry of Health set up centers in Hatay, Adana, Mersin and and other at-risk provinces for premarital screening and counselling in genetics. Here, we report the organization of the premarital screening program, the follow-up of the at-risk couples and the cost-effectiveness of the program in the province of Mersin. We have evaluated the results of the five-year screening program.

MATERIALS and METHODS

The region investigated was the province of Mersin, located in the southern part of Turkey on the Mediterranean Sea comprising coastal and mountainous areas and with a population of 1,515,607 in 10 counties.

The Center: The Muzaffer Aksoy Thalassemia Center, founded in February 1998, is organized under the auspices of the Mersin provincial health authorities. The Center began serving the province in February 1999 in a building that is strictly independent of any hospital to keep the premarital referrals separate from the patients.

Subjects: Couples intending to marry are sent to this unit. Voluntary participation is advised to any accompanying persons or relatives and to previously married couples. The screening is open to the public. A trained physician informs each couple about SCA and thalassemia, the carrier status and the risk of having a sick baby if both are carriers, and the importance and necessity of the test. They are then sent to the laboratory.

Stations in the Counties: In each county, a station was established at the largest district health center and was staffed with a general practitioner and two nurses. Premarital couples were directed to these stations and were informed about hemoglobinopathies by the trained physician, and blood samples were taken into EDTA and were duly sent to the Center within two to three days in cold chain. The results were given to the couples within a week with counselling and the at-risk couples were informed regarding the reproductive options and the availability of prenatal diagnosis. The Center carried out the follow-up of pregnancies.

Methodology: A total of 79,000 persons, including 31,498 premarital couples, were investigated from February 1999 to February 2004. Blood was taken into EDTA and red cell indices were done in Coulter AcT. In cases with mean corpuscular volume (MCV) ≤80 fl, HbA_2 and HbF were determined by column chromatography and alkali denaturation, respectively. Hemoglobin electrophoresis was carried out on cellulose acetate and agar gel. The sickling test was done to differentiate HbS from HbD. Cases with MCV<80 fl, HbA_2≥3.5% and HbF≥2% were considered to have β-thal trait. Those cases with normal HbA_2 with MCV<80 fl and HbAS with MCV<80 fl were sent for further evaluation to hematology clinics.

Action: If the couples were both carriers of an abnormal hemoglobin or β-thal, they were informed confidentially of their test results and counselled on reproductive options and on obtaining prenatal diagnosis. They were asked to come to the center in the case of pregnancy and with counselling were referred to the prenatal center at Cukurova University.

Table 1. Premarital screening of hemoglobinopathies in the province of Mersin

Country	*Population*	*n*	*AS**	*AS*	*Aβ thal*	*AD*	*AE*
Mersin	796,785	46,198	105	710	820	82	23
Anamur	79,964	5,483	-	4	210	11	6
Aydincik	11,363	824	-	-	9	-	-
Bozyazi	22,522	-	-	-	-	-	-
Camliyayla	9,752	666	-	-	16	1	-
Erdemli	112,267	8,011	1	7	188	11	2
Gulnar	29,943	2,824	-	2	37	6	-
Mut	58,397	5,190	-	1	119	14	-
Silifke	101,812	8,812	3	8	168	9	1
Tarsus	312,961	992	6	52	23	1	-
Total	1,515,607	79,000	115	784	1,590	135	32

AS*: HbAS with MCV ≤80 fl.

Other Hemoglobinopathies	
HbS β-thal	21
Hb SE	1
Hb SS	19
Hbβ-thal.β-thal	1
HbA α-thal	4
Hb AJ	1
HbD α-thal	1
HbAF (infants)	18
Total	66

RESULTS

In the five-year period, 31,498 couples (a total of 79,000 persons) were screened for hemoglobinopathies in the province of Mersin. The distribution of hemoglobinopathies is presented in Table 1. The rate of sampling seems to be well represented in all counties except Tarsus and Bozyazi. In the municipality of Tarsus county, where premarital screening was previously performed independently from the Ministry of Health, the referrals were fewer than expected since this county joined the program later. Also, in Bozyazi, all of the referrals preferred to go to Anamur. The carrier rates of HbS and of β-thal were found to be 1.21% and 2.04%, respectively. Hemoglobin AD was 0.17% and Hb AE, which was not rare, was 0.04%. In Mersin and Tarsus counties, HbS seems to be prevalent, at 1.8% and 5.8%, respectively. However, β-thal seems to be present in all counties, ranging from 1.0% to 3.8%.

Table 2 demonstrates the distribution of the types of hemoglobinopathies and the status of health insurance of at-risk families. One hundred thirty-four couples were found at-risk for a homozygous baby. One was found to be a misdiagnosis, HbAβ-thal/α-thal. We found 58.9% and 20.8% of the couples to be at-risk for HbS and β-thal, respectively. The percentage of the at-risk families that had some kind of health insurance (civil servants' fund or social security) was 67.2%, but 23.1% had no health insurance. The remaining 9.7% could not be reached due to change of address, thus no information was available regarding existence or not of pregnancy in these individuals.

The results of the follow-up of these couples are shown in Table 3. In 27 couples, no pregnancy had been reported, six couples were divorced, and 11 couples could not be reached due to change of address. Of the 135 pregnancies, 80 had prenatal diagnosis. Some families sought

Table 2. Type of hemoglobinopathy and health insurance status of at-risk families

Type	*n*	*Social Security*		
		Yes	*No*	*Unknown*
AS/AS	79 (58.9%)	53	19	7
Aβ-thal/Aβ-thal	28 (20.8%)	19	7	2
Aβ-thal/AS	14 (10.4%)	9	3	2
Sβ-thal/AS	6	4	1	1
Sβ-thal/Sβ-thal	1	1	-	-
AS/AE	1	1	-	-
AS/SS	4	2	1	1
ββ-thal/Aβ-thal	1	1	-	-
Total	134	90	31	13
%		67.2	23.1	9.7

Note: Total number of at-risk families:134
Misdiagnosis:1 (Aβ-thal/Aα-thal)

Table 3. Follow-up of the at-risk families between February 1999-February 2004

		Type of Hemoglobinopathy		
	Total	*AS/AS*	*Aβ/Aβ*	*Other*
Non-Pregnant	27	16	4	7
Divorced	6	5	-	1
Can not be reached	11	3	3	5
Sought prenatal diagnosis	80			
Abortus				
Elective manipulation	14	9	4	1
Spontaneous	5	3	-	2
Birth				
Normal	18	11	3	4
Carrier	32	24	4	4
Homozygous	1	-	1	-
Still	-	-	-	-
Late referral (homozygous)	1	1	-	-
Results not known	9	7	2	
Did not seek prenatal diagnosis	55			
Birth				
Normal	3	2	-	1
Carrier	10	6	3	1
Homozygous	18	7	8	3
Still	5	2	:	?
Results not known	19	3	10	6

prenatal diagnosis after having a sick baby. Two homozygous babies were born even after the prenatal diagnosis. However, 18 homozygous babies and five stillbirths were noted in couples that did receive prenatal diagnosis.

DISCUSSION

Diligent premarital screening is important in Cukurova, the southern part of Turkey where the high prevalence of hemoglobinopathies is evident, as documented in previous studies [1-11]. As seen in Table 1, Mersin and Tarsus counties are foci for the sickle cell gene. The reason for the high rate is attributed to the presence of Eti-Turks, an Arabic-speaking ethnic group in these aforementioned counties [1-11], whereas the β-thal gene was detected in all of the counties of Mersin at a considerable rate. The carrier rate for HbD was 0.17% and for HbE 0.04%. It is evident that in this large screening program, cases with normal MCV, double carriers of β- and α-thal trait and atypical forms of β-thal trait will be missed. A point to note is the high percentage of at-risk families for HbS as compared to β-thal. Of the 134 couples at-risk for a hemoglobinopathy, 80 were at-risk for HbS compared to 28 for β-thal (Table 2). The reason for this discrepancy is most probably due to the attitudes of this Arabic-speaking ethnic group. It is a closed community among which the rates of consanguineous marriages and multiparous births are high. Six couples were divorced on grounds of incompatibility. Eleven couples could not be reached because of address change. Only 58.9% of pregnancies were pre-diagnosed (Table 3). Two couples that had prenatal diagnosis and were informed gave birth to homozygous babies: one was a late referral by the obstetrician (over five months), and the other due to religious attitudes of the mother-in-law. The lack of prenatal diagnosis in 41.0% can be attributed to the lack of a financing social security (only 67.2% had health insurance), to the lack of sufficient

knowledge on heredity and the course of these debilitating diseases and to the illiteracy and the cultural background of the families [10]. A 15-20 minute genetic counselling seems insufficient for those who are informed of these diseases just before phlebotomy or when they receive the test results. These data show that the public is not well informed about these genetic diseases. Enlightenment of the public and the support of government are the leading criteria for the preventive measures. The meaning of the carrier status should be made well known to the public long before the age of marriage. As noted by Modell, Cao, Mitchell and Loutradi-Anagnostou, co-operation of the government and non-government organizations, leaders in the community, parent organizations at schools, religious leaders and local health personnel are the prerequisites for the education of the public in this regard. With the help of these organizations, along with premarital screening programs, few affected births were realized in recent years in the United Kingdom, Italy, Canada and Cyprus [24-28]. Scriver's group achieved almost 90-95% success in informing high school students utilizing similar organisztions, voluntary screening and genetic counselling over a 20-year span in Canada [27]. In the United Kingdom, the utilization of prenatal diagnosis, which was 20% from 1974-1994, had risen to 80% by 2000 [16,25].

In this screening survey, 20 homozygous babies would possibly not have been born if the couples had been well informed, had health insurance coverage and had been given the opportunity of prenatal diagnosis in all pregnancies. The cost of prenatal diagnoses for HbS is $500, and for β-thal and HbS/β-thal cases is $1000. Thus, the total cost would have been $94,500. Considering the screening survey cost as $5 each, the cumulative cost for screening and prenatal diagnosis would have been $409,480. If we consider the cost of the medical expenses for the affected baby as averaging $10,000 per annum, the expense of the preventative measures appears well spent. Thus, it is the moral responsibility of the carrier couples to not have affected babies, both from the psychological point of view of the child as well as for themselves.

In conclusion, this study reveals the need for an education program along with the screening. An extensive and intensive education program for general practitioners and obstetricians should be given in at-risk areas. A healthy population in the future can be achieved via improved education regarding these diseases and through shared responsibility between the public and the government.

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