Sickle Cell Anemia in Northern Israel: Screening and Prevention

Ariel Koren MD[1,5], Lucia Zalman PhD[2], Haya Palmor BSc[2], Ronit Bril Zamir MSc[3], Carina Levin MD[1,5], Ariella Openheim MD[6], Etty Daniel-Spiegel MD[4], Stavit Shalev MD[3,5] and Dvora Filon PhD[6]

[1]Pediatric Hematology Unit and Department of Pediatrics B, [2]Hematology Laboratory, [3]Human Genetics Unit and [4]Department of Obstetrics and Gynecology, HaEmek Medical Center, Afula, Israel

[5]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

[6]Department of Hematology, Hadassah Medical Center and Hadassah-Hebrew University Medical School, Jerusalem, Israel

ABSTRACT: **Background:** Sickle cell anemia is a hemolytic anemia caused by a single mutation in position 6 of the β globin molecule. About 80 patients with SCA in northern Israel are currently receiving treatment.

Objectives: To assess a screening program in northern Israel aimed at detecting couples at risk for having offspring with SCA.

Methods: Since 1987, screening for β thalassemia in pregnant women in northern Israel has been conducted, and from 1999 all the samples were also tested for hemoglobin S, Hgb C, Hgb D, Hgb O Arab and others.

Results: During the 20 year period 1987–2006 a total of 69,340 women were screened; 114 couples who carried Hgb S were detected and 187 prenatal diagnoses were performed in couples at risk for having an offspring with Hgb S. The mean gestational age was 13 ± 4 weeks. Fifty-four of those diagnoses revealed affected fetuses and in 4 cases the couple declined to perform therapeutic abortion.

Conclusions: The economic burden to the health services for treating SCA patients is about U.S.$ 7000 per year, and the institution of prevention programs has proven cost-effective in populations with a high frequency of carriers. Since our program is aimed to also detect β thalassemia, a disease that is more frequent in this area (› 2.5%), the added cost for the prevention of SCA is less significant despite the low incidence of the S gene in our population, namely ‹ 1%.

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KEY WORDS: sickle cell anemia, prevention, screening

Sickle cell anemia is a hemolytic anemia caused by a single mutation in position 6 of the β globin molecule. The clinical picture of SCA is characterized by diverse types of crises, such as vaso-occlusive crises, acute chest syndrome, central nervous system infarcts, hemolytic and aplastic crises, avascular necrosis of hip, and acute splenic sequestration. SCA is transmitted in an autosomal recessive manner and in addition to the homozygous SS compound, heterozygosity with other diseases of hemoglobins such as β^+ or β^0 thalassemia, Hgb C or D can cause a similar clinical presentation.

The Hgb S gene originated in Central Africa and dispersed to the population of African origin in the Americas. The Hgb S mutation also dispersed to India, Saudi Arabia and the Mediterranean basin by the slave trade and Bedouin nomads. In Israel the SCA gene is found among tribes of Bedouin origin, principally in northern Israel [1-5] and in one village located on the coast where African slaves settled several hundred years ago. SCA carriers are resistant to malaria, therefore the gene prevalence is high in those areas where malaria was common until the beginning of the 20th century. Malaria was common in northern Israel, the northern coast (Mediterranean Sea), the Jezreel Valley and the Hula Valley [1-3]. In this area about 80 patients with sickle cell disease are treated in several hematology units, half of them having SCA and the other half sickle cell β^+ or β^0 thalassemia. Recently SCA was also recognized among foreign workers of African origin living in large cities in central Israel [6].

Sickle cell trait, the heterozygous state, presents with a normal phenotype without clinical symptoms or signs and with normal blood count. In such cases, carrier detection is not possible based on clinical findings or pathognomonic features in red cell indexes such as seen in thalassemia carriers. Only ethnic origin or family history can raise the suspicion of a SCA carriership. The final diagnosis of a carrier is based on Hgb electrophoresis or high performance liquid chromatography.

Since 1987, screening of pregnant women for β thalassemia has been carried out in the Jezreel Valley and during the past two decades the program was extended to almost all northern areas of Israel, areas where malaria was present and where the SCA gene is present in Bedouin tribes. Originally, the program design was based on screening red blood cell indexes and Hgb electrophoresis, which was performed only in those samples suspected of being β thalassemia carriers. Since 1999 with the introduction of the Variant Hgb testing system (Biorad, USA) and HPLC analysis, the program design has changed and all

SCA = sickle cell anemia

HPLC = high performance liquid chromatography

the samples are tested for the detection of abnormal hemoglobins including Hgb S, Hgb C, Hgb D and Hgb O Arab [7].

In this paper we summarize the results of this preventive program aimed at detecting couples at risk for having offspring with SCA, including compliance with genetic counseling and prenatal diagnosis, and report the incidence of affected babies who were born.

PATIENTS AND METHODS

The program for prevention of hemoglobinopathies in northern Israel, instituted in 1987, covers the northern part of Israel, including the Jezreel valley, the Nazareth area, the upper Galilee, the Hula valley and the northern coastal region [7]. The overall population in the north numbers about a million, and approximately 50% are of Arab ethnic origin. A significant percentage of them are of Bedouin origin, a population for whom, at least in part, an African origin can be demonstrated [8].

The blood samples were taken by nurses at the Mother and Child Health Care clinics throughout the area. The blood samples were all analyzed at the Hematology Laboratory at HaEmek Medical Center (L.Z. and H.P.).

In the first period, until 1993, the program covered a small area, but since 1993 the area was gradually enlarged to the regions described above. From 1987 until 1999 the program was designed to detect only β thalassemia carriers. The blood samples were analyzed by the Technicon H1 and later the Technicon H2 automatic blood counters; only samples with a mean cell volume < 78 fl and/or mean cell hemoglobin < 27 pg were further analyzed by Hgb electrophoresis (agarose membrane electrophoresis and by Hydrosis Sebior, France). When a woman was found to be a β thalassemia carrier, her husband was analyzed by a blood count and Hgb electrophoresis independent of the red cell indices in order to detect Hgb S carriers. During those years sickle cell carriers were detected only by family history or when the mother was found to be a β thalassemia carrier and her partner a sickle cell carrier. Since 1999 when a Variant Hgb testing machine (Biorad Co., USA) was introduced, all the samples underwent complete blood count analysis and HPLC-cation exchange analysis in order to detect abnormal hemoglobins like Hgb S, C and D, in addition to Hgb A, F and A2 [Figure 1].

If a woman was identified as a carrier of abnormal hemoglobin, her husband's blood sample was requested. All partners' blood samples were analyzed by HPLC. If both partners carried abnormal hemoglobin, the couple was referred to genetic counseling (R.B.Z. and S.S) and prenatal diagnosis was offered.

Prenatal diagnosis was performed at HaEmek Medical Center by means of chorionic villi sampling or amniocentesis according to gestational age and the couple's preference. DNA analysis was performed at the Hematology Laboratory, Hadassah Medical Center (D.F. and A.O.). In the early years of the project (1987 and 1988), prenatal diagnosis was performed by umbilical venous blood sampling and globin chain synthesis analysis. Prenatal diagnosis was performed in pregnancies of couples identified as carriers by the screening program or in couples with a previous affected child. The results are pooled together.

Figure 1. The screening program for hemoglobinopathies – Algorithm

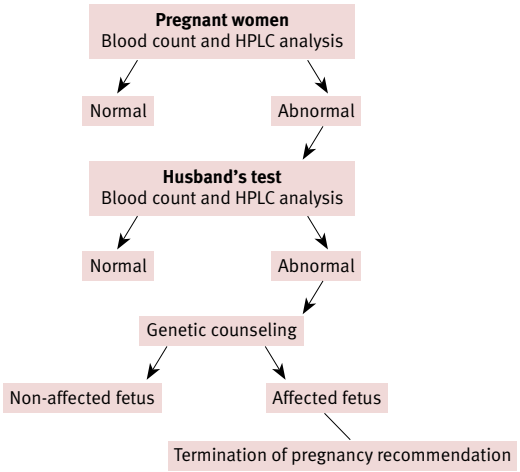
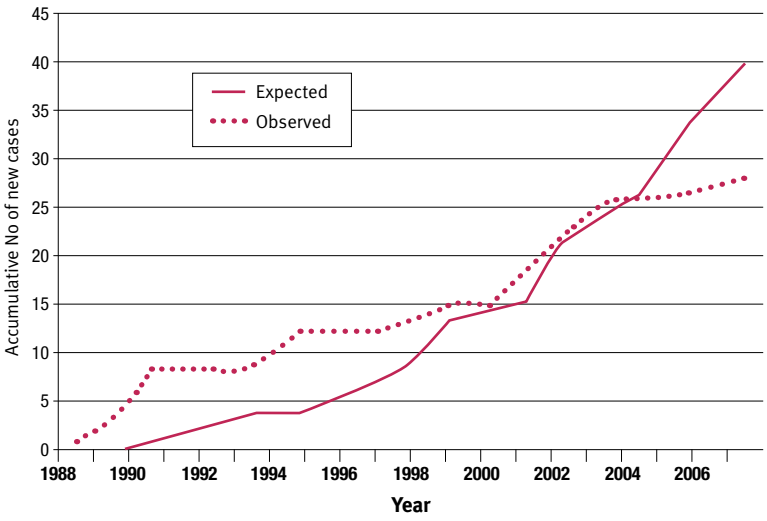


Figure 2. Sickle cell anemia prevention: expected vs. observed cases, 1988–2006



BENEFITS OF THE PROGRAM ACCORDING TO CARRIER DETECTION

The number of newly diagnosed patients was calculated as the number of newly diagnosed patients compared to the total number of patients who would be estimated to be born if a prevention program was not instituted [Figure 2].

RESULTS

The area covered by the screening program was enlarged several times. At the beginning, from 1987 until 1992, only the Jezreel valley area was covered by the program. This area included the cities of Afula, Nazareth, Migdal HaEmek and Beit Shean and all the rural surroundings. The population is heterogeneous, comprising both Jews and Arabs. Since 1993 the Eron valley area was included, an area whose population is mostly Arab. Subsequently, the Upper Galilee area was also included in the program and from 2005 the area surrounding the city of Hadera, on the coast, were also covered by the program. This area includes three large villages populated by inhabitants of Arab origin. Based on previous knowledge, at least one of those villages included a large population of African origin, with a high frequency of sickle cell carriers.

The total number of pregnant women screened by the program from July 1987 to December 2006 was 69,340. In the first period, 1987–1992, when the program covered only the population in the Jezreel area, a mean of 1700 ± 496 analyses were performed each year. From 1993 to 1998, before the period when the program design was changed from the intention to detect only β thalassemia carriers to the universally HPLC analysis, the mean number of analyses per year was 2900 ± 506. From 1999 until 2004, the number of woman screened per year rises to a mean of 4295 ± 639 and from 2005 when the geographic area was enlarged and several other large Arab villages were included, the number of tests rises to a mean of 7200 per year.

COUPLES DETECTED [TABLE 1]

During the period 1987–1998, 51 couples carrying Hgb S were detected (mean 4.25 couples/year), 26 couples were combined β thalassemia and sickle cell carriers, and in 21 couples both parents were found to be sickle cell carriers. Two other couples comprised a carrier of sickle cell and a partner affected with sickle cell β thalassemia, and in two couples a combination of Hgb C and Hgb S was found. From 1999 to 2006 a total of 63 couples at risk were detected (mean 7.8 couples/year). In 39 couples both parents were carriers of sickle cell, 19 couples carried the β thalassemia and the sickle cell gene, and three couples carried Hgb C and Hgb S. One other couple carried Hgb S and Hgb Knososs. In another couple the pregnant woman carried Hgb S and her husband's analysis revealed red blood cell indices consistent with the thalassemia trait. Further analysis revealed an undefined abnormal hemoglobin fraction by HPLC, but α and β gene sequencing did not reveal any disease-causing mutations. Prenatal diagnosis was not performed in those two couples.

Five couples carried a combination of Hgb S and an α globin mutation, a combination that is not predictive of significant medical consequences, therefore prenatal diagnosis was not discussed.

The total number of couples at risk detected by the program was 383 including 141 β Thal/β Thal and 20 Hgb C; another 86 couples were found to be carriers of α thalassemia in both parents or combined α with β thalassemia. Hgb O Arab combinations were found in seven couples, including four couples of whom both parents carried this abnormal Hgb. Since medical consequences were not predicted to be of significance, prenatal diagnosis was not recommended to those couples. Several other rare combinations were found in the other couples.

PRENATAL DIAGNOSIS

During the years 1987 to 2006 a total of 492 prenatal diagnoses for hemoglobinopathies were performed, including 187 tests of couples at risk for having an offspring with Hgb S (homozygous sickle cell, sickle cell β thalassemia, SC or SD disease). The mean gestational age at first genetic consultation was 13 ± 4 weeks (range 7–29 weeks). Only 13 of those prenatal diagnoses were performed in 6 women who were referred because of a previous affected child. The results of the prenatal diagnosis are presented in Table 2. Fifty-four of those diagnoses revealed affected fetuses, and in 4 cases the couple declined therapeutic abortion and affected babies were subsequently born. In three of those cases the prenatal diagnosis was performed at gestational age 11, 15 and 19 weeks; in the fourth one the data were not available. In one pregnancy, prenatal diagnosis was performed in 1988 after UVS (umbilical venous blood sampling) and a false negative diagnosis was probably made since the child died at home before the age of 1 year with a clinical picture that was highly

SC = sickle cell Hgb C disease
SD = sickle cell Hgb D disease

Table 1. Sickle sell anemia screening: couples at risk detected

Diagnosis (couples at risk)	Period 1987–1998 (12 yrs)	Period 1999–2006 (8 yrs)	Total no. of couples at risk detected (20 yrs)
Hgb S + Hgb S	21	39	60
Hgb S + α thalassemia	26	19	45
Hgb S + Hgb C	2	3	5
Hgb S + sickle cell β thalassemia	2	–	2
Total no. of couples at risk	51	61	112
No. of couples detected/year	4.25	7.8	6.0
Couples not at risk			
Hgb S + β thalassemia	ND	5	5
Hgb S + Hgb Knossos	–	1	1
Hgb S + undetected Hgb	–	1	1

ND = not done.

Table 2. Prevention of sickle cell anemia: methods and results of prenatal diagnosis

Method of prenatal diagnosis	**Total***		
Umbilical vein sampling	7		
Amniocentesis	66		
Chorionic villi sampling	113		
Results of prenatal diagnosis		**Parents' diagnosis**	
Prenatal diagnosis	**Total**	**Hgb S/Hgb S**	**Hgb S/β Thal**
Sickle cell trait	76	55	21
β thalassemia trait	16	–	16
Normal	36	24	12
Sickle cell disease	29	29	–
Sickle cell β thalassemia	25	–	25
Others (Hgb C – Hgb D)	4**	–	–

* 1 case: data not available.
** Hgb C Trait: 3, Hgb SD disease: 1.

suspicious for acute splenic sequestration. Unfortunately, no Hgb electrophoresis or other laboratory analyses were performed to confirm the diagnosis. One spontaneous abortion and one antepartum fetal death occurred among the 187 pregnancies that were tested (1%). In both cases the fetuses were previously diagnosed as Hgb S homozygous.

INFLUENCE OF THE SCREENING PROGRAM ON NEWLY DIAGNOSED PATIENTS

During the period 1987–1998, when the program was conducted for the detection of β thalassemia carriers based on red cell indexes, the number of new cases diagnosed every year exceeded the number of prevented cases. Afterwards, during the first 5 years of the modified program (1999–2004), when the routine analysis also enabled the detection of Hgb S carriers, the number of new cases was similar to the number of expected cases based on the disease prevalence, but later the number of new cases decreased significantly compared with the number of expected cases that would be born with no screening program [Figure 1].

DISCUSSION

Since 1987, screening for β thalassemia in pregnant women has been conducted in northern Israel, and over time the program was extended to almost all the northern areas of Israel. In this region malaria was present until the beginning of the 20th century and the SCA gene was found to be prevalent among tribes of Bedouin origin living in this area. Since 1999, with the introduction of the Variant Hgb Testing system (Biorad, USA) and HPLC analysis, the screening program design was changed and all the samples were tested for the detection of abnormal hemoglobin, including Hgb S, Hgb C, Hgb D and Hgb O Arab.

During the 20 year period 1987–2007 a total of 112 couples at risk for having a child with sickle cell disease were identified. The couples detected during the first 12 year period of the screening program are classified into two groups: woman who carried the β thalassemia gene and were detected by the original screening program and subsequently their husbands were found to be Hgb S carriers, or women with a family history of Hgb S. In the beginning, the study design was not aimed to detect Hgb S carriers among pregnant women since the initial screening was based on red blood cell indexes concomitant to the thalassemia trait and hemoglobin electrophoresis performed only in those women with red cell indexes suggesting a β thalassemia carrier status. In the next 8 year period, the program design was directed to detect not only thalassemia carriers but also Hgb S carriers were routinely detected since an HPLC analysis was performed in all samples. The area covered by the program was also slowly enlarged to include some areas with a known high frequency of Hgb S carriers. Consequently, there was an increase in the incidence of at-risk couples detected, from 4.25 per year in the first period of the program to 7.8 per year in the second. This increase in detection rate can be attributed not only to the change in the program design but also to the inclusion of a population with a high incidence of Hgb S carriers.

The real frequency of carriers in the population screened cannot be deduced from these data, since personal observations found the incidence of the S gene to be significantly variable between different communities or villages. Hgb S is common among Bedouin individuals and in populations of African origin, but it is not present in the Jewish population, including Ethiopian Jews or in an Arab population not of Bedouin origin. The frequency of carriers in the whole cohort of pregnant women screened is 0.88%; no other data are available with regard to the frequency of Hgb S carriers in the general population in the area covered by the program. Another factor that raised the number of carriers in some Arab villages is the high level of consanguinity, a tradition that is deeply rooted in this population, especially in rural areas where families maintain an isolated community lifestyle. In Greece the mean frequency of Hgb S carriers is about 1%, but those carriers are concentrated in certain areas of the country, like the concentration of Hgb S carriers in our country [4,5,9]. The screening in Greece is offered voluntarily by the health authorities, army medical services and others, but no general population screening seems to be practiced today. Also in Europe, because of the immigration of high risk African populations, programs of carrier detection of pregnant women were recently instituted and have a high incidence of acceptance. In one study from The Netherlands the incidence

of Hgb S carriers was about 2.5% among immigrants and no carriers were found in the native Dutch population. That study included only 42 women of non-Dutch origin [10]. In Saudi Arabia a premarital screening approach was preferred, probably due to religious edicts that oppose termination of pregnancy. In that country 4.2% of the screened individuals were carriers of the Hgb S gene. In spite of the premarital screening, about 90% of the couples in Saudi Arabia found to be at risk for having an affected offspring decided to marry despite the known carrier status [11].

The mean gestational age at the first genetic consultation, 13 ± 4 weeks, allowed the couples to accept the recommendations that were discussed during the genetic counseling. Prenatal diagnosis and further termination of pregnancy was performed in 40 of the 45 affected fetuses detected, revealing a 90% acceptance. Since the gestational age in those couples that preferred not to perform therapeutic abortion was 11, 15 and 19 weeks, we cannot deduce that this was a relevant factor in their decision. The gestational age at which the prenatal diagnosis is offered to couples is important in terms of acceptance. In a study performed in London, 82% of pregnant women requested prenatal diagnosis when the mother was seen in the first trimester of pregnancy compared to only 49% when the prenatal diagnosis was offered during the second trimester [12]. Another study from central America found that gestational age at the time of counseling together with the existence of an affected child in the family were the most important factors in the acceptance of prenatal diagnosis [13].

In one case a wrong diagnosis was probably made. A child with normal prenatal test died at home under the age of 1 year, due to a clinical picture that could resemble acute splenic sequestration, as reported by the mother.

In the last 4 years of the prevention program, a significant decrease in new affected babies was observed. It may be due to improved awareness by the population as a result of the program, or to the primary caregivers who referred pregnant women early for screening and allowed early counseling and prenatal diagnosis.

It is important that such a screening program be conducted by a team that includes dedicated and well-trained nurses in the community, an experienced hematology laboratory with experts in the detection of abnormal hemoglobin, and a genetic consultant team that can provide clear explanations and ensure that the couples are fully informed regarding their risks and their reproductive options. Also required is a consultant hematologist experienced in the treatment of sickle cell disease who can give professional support to the laboratory personnel and to the genetic counselors, in particular when questionable cases arise. The success of such a program is also totally dependent on efficient coordination and systematic management of all the efforts in order to achieve good results.

Sickle cell anemia is presently regarded as a treatable disease, and since the introduction of hydroxyurea treatment, trans-cranial Doppler screening and further regular transfusions in order to prevent cerebral infarctions, the quality of life of affected individuals has improved significantly. Subsequently, the issue of prenatal diagnosis and termination of affected pregnancies should be re-discussed and evaluated with the couples at risk. Several studies summarized the experience of acceptance of termination of affected pregnancy in families with SCA. In the Indian study all the couples with affected fetuses opted for pregnancy termination [14]. Also among couples from Gaza and the West Bank [15] and Nigeria [16], termination of pregnancy was also accepted. We believe it important that personnel experienced with treatment of SCD be part of the genetic counseling team in order to discuss with the couple the implications of having a child with SCA [17] and help them to reach a well-informed decision.

Another issue that should be discussed with the couple at risk is the diverse clinical severity of SCA. While some individuals have a mild clinical course, others might present a severe form, with no reliable predictive tool to assist the counselors or the counselees during the pregnancy. The combination with the α gene mutation may induce high Hgb F production and a resultant mild disease course. Presently, the life expectancy of SCA-affected individuals is 14 to 20 years less than the life expectancy in the general population of the same area [18] or a median age of 44 years according to other reports [19]. This survival rate may improve with better medical treatment, including hydroxyurea and stroke prevention. The resultant approach to prenatal diagnosis and termination of pregnancy may change significantly in the next few years. Proper care after birth should be assured to the couple who choose to have a child with SCA, after a comprehensive explanation in understandable language has been given [20].

The economic burden to the health services providing hospital treatment to SCA patients is high, about $7000 per year [21], and the institution of prevention programs has proven cost-effective in populations with a high frequency of carriers [22]. Since our program is aimed at detecting also β thalassemia, which is much more frequent in the area covered by the program (> 2.5%), the added cost of the prevention of SCA is less significant in spite of a low incidence in our population, < 1%, an incidence not considered cost-effective for the institution of a prevention program [22].

Correspondence:
Dr A. Koren
Dept. of Pediatrics B, HaEmek Medical Center, Afula 18101, Israel
Phone: (972-4) 652-5576
Fax: (972-4) 652-5589.
email: koren_a@clalit.org.il

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