Screening for Genetic Disorders among Jews: How should the Tay-Sachs Screening Program be Continued?

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Abstract

The screening program in Israel for Tay-Sachs disease has proven very successful, giving Jewish couples a choice not to have affected children. The technology of carrier detection is now possible in several other severe genetic diseases that are relatively frequent among Jews. Due to the current confusion, a policy is needed to determine how the TSD screening program should be continued in the Israeli Jewish population. We propose that such a screening program include only mutations agreed by consensus as causing a disease severe enough to warrant the possibility of therapeutic abortion. We also propose that general screening include only mutations that are relatively frequent, taking into account the carrier frequencies in the Israeli Jewish population.

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The Tay-Sachs disease prevention program was initiated in 1971 among Jews of Ashkenazi origin according to the principles first formulated for the World Health Organization by Wilson and Jungner in 1968 [1]. Indeed, the program met the critical prerequisites, namely, that: a) the disease is severe and occurs predominantly in a well-defined population; b) it is possible to detect heterozygotes by a simple, accurate and inexpensive technology, i.e., enzymatic determination; and c) it is possible to diagnose the disease *in utero* early in the course of pregnancy [2]. In Israel, the TSD program was offered to Jews of Ashkenazi origin, who represented the largest Jewish community at the time. However, during the following years it was found that TSD is also relatively frequent among Jews of Moroccan origin, the largest non-Ashkenazi Jewish population in Israel [3]. The program was therefore expanded to include this community, but in fact is open to everyone free of charge.

The confusion

The screening program has proven extremely successful, giving Jewish couples a choice not to have affected children. As a result, the frequency of TSD among Jews has been dramatically reduced [4]. While the carrier frequency among the Ashkenazi and Moroccan Jews remains relatively high, several recent developments point to the urgent need for a policy decision on how to continue the screening program. This will be dealt with later in the article.

During the last decades it was demonstrated that in addition to TSD, other genetic diseases are relatively frequent among Jews worldwide, some of which are amenable to the technology of carrier detection. As a consequence, pilot studies have been initiated among Ashkenazi Jews in the USA to screen for carriers of cystic fibrosis and, in various combinations, for Gaucher, Niemann-Pick type A, Bloom and Fanconi syndromes, in addition to the screening for TSD [5,6]. In the last few years, similar screening programs that are targeted mainly at Ashkenazi Jews were also introduced in Israel and offered to couples on a private payment basis. These "private screening programs" have led to considerable confusion not only for health professionals, but also for the general public that lacks comprehensive information on the subject. Adding to the confusion was the recent inclusion of some of these tests in the supplementary insurance provided by the health maintenance organizations (sick funds). Clearly, a decision as to whether to include these screening programs in the "basket of services" covered by the National Health Insurance Law mandates an informed presentation of the geneticists' recommendations on the programs and their cost effectiveness.

A fundamental question to be addressed before introducing a national carrier-screening program is the *relative incidence of the disorder in the population*. With the progress of the Human Genome Project, the ability to detect carriers of most genetic diseases, even those that are very rare, will be available in the near future. This is an outcome of both the accumulation of knowledge and the development of new technologies. Given this scenario, there are some who will argue that a test already being performed to detect carriers of *relatively frequent* diseases should also be used to diagnose carriers of *rare* disorders for which such testing is possible. However, it should be remembered that even when the rate of detection is optimal, false positive/negative results may occur; thus, the overall possibility of an error, especially in very rare diseases, may be higher than the chance of identifying a carrier.

TSD = Tay Sachs disease

Many disorders have been found to be relatively frequent in different Jewish communities [Table 1]. In Israel however, a new situation has evolved due to the increasing tendency for marriages in which each spouse comes from a different Jewish community. It is expected that within the foreseeable future a large proportion of the Jewish population in Israel will be of mixed origin. Accordingly, the carrier frequency for diseases that were limited to one community has begun to decrease, while at the same time the size of the population at risk is increasing, leading to new carrier frequencies of genetic diseases. For instance, while the carrier frequency of TSD is 1/30 among Ashkenazi Jews and 1/110 among Moroccan Jews, representing approximately 35% and 18% respectively of the Jewish population in Israel, mixed marriages will create a new carrier frequency of around 1/60 among Israeli Jews. Similarly, for disorders that are relatively frequent in small communities only, the carrier frequency in the general Jewish population will be much lower. For example, the carrier frequency of metachromatic leukodystrophy, which is 1/50 among Jews from Yemen, will decline to as low as <1/500 in a mixed Jewish population. Therefore, for those disorders that are frequent in relatively small communities or those present in larger communities where the frequency is not so high, the mixing of the population will lead to frequencies that probably do not justify screening.

The other important question that should be addressed is the goal of the screening. Taking for example the neonatal screening program for detecting phenylketonuria and hypothyroidism, the objective is clear: to allow for preventive treatment. Unfortunately, this is not yet possible for the majority of genetic diseases. Nonetheless, it has been found that an effective way to reduce the impact of genetic diseases is by primary or secondary prevention. In primary prevention, screening is used for premarital counseling. The ultra-orthodox Jewish community is an example of a successful primary prevention program. Almost all marriages among this community are prearranged, and since terminating a pregnancy is unacceptable, screening is aimed at detecting couples at risk of passing on a genetic disorder before the engagement and thereby preventing marriages between heterozygotes [7]. This kind of genetic screening was willingly adopted by the ultra-orthodox community with the cooperation and blessing of its religious leaders, since it meets their needs without contravening their religious beliefs. In contrast, secondary prevention offers potential couples at risk the accessibility of prenatal diagnosis and/or interruption of the pregnancy if the fetus is affected. Thus, since marriage among the majority of the Israeli population is not prearranged but by choice, the average couple prefers to participate in a genetic test only after marriage in order to prevent the future birth of an affected child. In view of the fact that the only way to achieve the purpose of such screening is by interruption of pregnancy, screening should be proposed only for tests with the potential to detect severe genetic disorders. Moreover, there should be a consensus within the target population that the severity of the disease is such that therapeutic abortion may be envisaged [8]. This was one of the major reasons for acceptance of the Tay-Sachs carrier screening among Ashkenazi Jews, including the religious community.

Table 1. Recessive genetic diseases relatively frequent among Jews in Israel according to ethnic origin

	Inheritance	Carrier frequency*
Most Jewish communities		
Fragile X	XLD	Variable**
Cystic fibrosis	AR	Variable
Thalassemia	AR	Variable***
Ashkenazi Jews (35% of Jews)		
Bloom syndrome	AR	1:110
Canavan disease	AR	1:60
Dysautonomia, familial$^{\infty}$	AR	1:30
Fanconi's anemia	AR	1:90
Gaucher disease type I	AR	1:15
Lipoamide dehydrogenase deficiency	AR	1:95
Mucolipidosis IV$^{\infty}$	AR	1:70
Niemann-Pick disease A	AR	1:80
Persistent hyperinsulinemic hypoglycemia of infancy	AR	1:160
Tay-Sachs disease	AR	1:30
Jews from Morocco (18% of Jews)		
11 beta-hydroxylase deficiency	AR	1:30
Ataxia telangiectasia	AR	1:80
Cystinosis	AR	1:100
Cerebrotendinous xanthomatosis	AR	1:70
Glycogen storage disease III	AR	1:35
Tay-Sachs disease	AR	1:110
Jews from Libya (3% of Jews)		
Creuzfeld-Jakob disease	AD	1:24,000
Limb girdle muscular dystrophy (LGMD2B)	AR	1:10
Jews from Iraq (6% of Jews)		
3-methyl glutaconic aciduria$^{\infty}$	AR	1:50
Thrombasthenia (Glanzmann)	AR	1:40
Jews from Iran (4% of Jews)		
Corticosterone methyl oxydase II deficiency	AR	1:30
Inclusion body myopathy$^{\infty}$	AR	Unknown
Polyglandular deficiency syndrome	AR	1:50
Jews from Yemen (6.5% of Jews)		
Metachromatic leukodystrophy	AR	1:50
Phenylketonuria	AR	1:35

Includes only diseases that may be severe. Excluded are mutations leading to an increased susceptibility to a severe disease (see ref. 11 for a complete list of Mendelian disorders among Jews). The percentages of the different communities in Israel are derived from a recent study of Jewish women who gave birth in 1990–91 (T. Cohen, personal communication).

$^{\infty}$* An estimate in most cases

** Particularly frequent among Jews from Tunisia

*** Particularly frequent among Jews from Kurdistan.

$^{\infty}$ Mutation(s)/gene still unknown.

AR = autosomal recessive, XLR = X-linked dominant, AD = autosomal dominant.

Genetic disorders that are relatively frequent in the Jewish population have different degrees of severity and morbidity. Among Ashkenazi Jews, the relatively frequent diseases that are lethal in early childhood and/or lead to severe disability are TSD, Niemann-Pick type A, Canavan

disease, Bloom syndrome, cystic fibrosis, familial dysautonomia, Fanconi's anemia and mucolipidosis IV. Among Jews of Moroccan origin, the relatively frequent diseases include TSD, cystic fibrosis, ataxia telangiectasia, cerebrotendinous xanthomatosis and cystinosis.

If indeed the recommendation would be to launch a national screening program targeted at preventing severe genetic diseases or disorders, the criteria of severity should include the relevant mutations and not only the clinical disease itself. In other words, the objective of the screening should be to detect all the mutations associated with a severe phenotype and not merely the carriers of all possible mutations. An example is a polymorphism in the CFTR gene that may cause agenesis of vas deferens. This mutation should not be included in a genetic screening of the general population, since the objective is not to detect fetuses at risk of infertility. Another example is non-neuronopathic Gaucher disease, a disease that is frequent in the Ashkenazi Jewish community. The most frequent mutation, N370S, is often associated with a mild type of Gaucher disease, while the second most frequent mutation, 84GG, is associated with severe disease. The frequency of the very mild form of the disease, the inability to predict the severity of the phenotype, and the existence of an effective treatment for this phenotype are among the arguments against screening for carriers of Gaucher disease in the Ashkenazi Jewish population [9,10]. Therefore, the possibility of screening for carriers of Gaucher disease, limited only to the particular mutations causing the severe form of the disease, should be considered.

Conclusions

In view of the above, how should the TSD screening program be continued in the Israeli Jewish population? What policy should be taken to avoid the existing confusion and enable an efficacious and ethical program? We propose that such a screening program include only mutations agreed by consensus as causing a disease severe enough to warrant the possibility of therapeutic abortion. The second issue is determining the minimal carrier frequency of such a mutation. Since the new policy will be aimed mainly at a mixed Jewish population, carrier frequencies in this population must be taken into account. In all cases it should be explained to couples that the goal of national screening is not to detect all possible disorders that may be diagnosed. Those couples who want information about other diseases and carrier states should be referred to a genetic counseling clinic, particularly at the present time when more than half the population still has a clearly defined origin.

Finally, while the principles discussed in this article are relevant for the entire population in Israel, the problems raised by a screening program for the detection of carriers of frequent genetic disorders among Arabs are different and will be discussed in a forthcoming article.

Note. This article represents the opinion of the authors and not necessarily those of the Ministry of Health.

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I always wait for The Times *each morning. I look at the obituary column, and if I'm not in it, I go to work.*

A.E. Matthews, English actor (1869–1960)