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Screening for Carriers of Tay-Sachs Disease in the Ultraorthodox Ashkenazi Jewish Community in Israel

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A screening program for the detection of Tay-Sachs disease (TSD) carriers in the ultra Orthodox community of Ashkenazi Jews has operated in Israel since 1986. The purpose of this program is the prevention of marriages of 2 heterozygotes. The screened individuals are mostly couples in the engagement process or students in religious high schools. Two mandatory requirements guide this program. First, anonymity of the tested individuals who are identified only by code numbers; second completion of the test results of couples in the engagement process within a few days. The screening program is performed by the determination of hexosaminidase A (Hex A) activity in serum which is repeated in serum and leukocyte extracts in couples where both partners were found in the heterozygote range in the initial tests.

The minimal carrier frequency was estimated to be 1:26 or higher, which is higher then in the general Jewish Ashkenazi population. This higher carrier frequency apparently stems from the fact that most members of this community originate from central Europe where the TSD carrier frequency was previously reported to be the highest in the Ashkenazi population. Since the beginning of the screening program no TSD child has been born to newlywed couples of this community in Israel.

KEY WORDS: Hex A activity, prenatal diagnosis, heterozygotes

INTRODUCTION

An important fraction of the Ashkenazi Jewish population, namely, the religious ultra Orthodox community, mostly does not participate in Tay-Sachs disease (TSD) screening programs due to religious restrictions regarding prenatal diagnosis and pregnancy terminations. Thus, in recent years, most of the TSD patients in Israel were born to families in this population group. In 1985 a not-for-profit organization ("Dor Yeshurim") was founded with the aim of identifying TSD carriers in the ultra Orthodox community before engagement and thus to prevent the marriage of 2 carriers. Because of the unique nature of this community the screening program had to meet 2 requirements, namely, anonymity of the individuals tested and rapid answers, unless the individuals had been tested previously. The need for rapid results stems from the fact that marriages are usually arranged by the parents and after the decision is made this is quickly announced in the community. The results of the TSD carrier tests must therefore be completed before the final announcement. These 2 requirements could not be met by the state sponsored programs currently operating in Israel, the United States, and other countries and therefore prevented the participation of this community in the screening programs.

This is the first report of the Dor Yeshurim screening program and its outcome in Israel.

MATERIALS AND METHODS

Enzyme Determinations

Hexosaminidase A (Hex A) was determined in serum or leukocyte extracts by 2 methods; heat inactivation or by the substrate 4 methylumbelliferyl-N-acetyl-glucosamine-sulfate (4MUGS, Research Development Co., Toronto, Canada).

For heat inactivation, serum is diluted 1:30 (v/v) by 0.05 M citrate-phosphate buffer, pH 5.0, containing 1 mg/ml Hex-free bovine serum albumin (Calbiochem–Novabiochem AG, Laufelfingen, Switzerland). Enzyme determinations were performed in triplicates, before and after heat inactivation at 50°C for 3 hours, according to O'Brien et al. [1970]. Leukocytes were prepared by the dextran heparin technique [Kampine et al., 1966]

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from 10 ml heparinized blood, and disrupted in physiological saline by 3 bursts of 10 seconds each of ultrasonication (Microson, Farmingdale, N.Y.). Hex A was determined as previously described [Vecht et al., 1983].

The second technique utilized 4MUGS which was demonstrated to be a specific substrate for Hex A [Kresse et al., 1981] and was introduced in our center for routine use in 1990. Although this substrate is less accurate than heat inactivation for heterzygote identification, individuals in the heterzygote range by both techniques together, namely by heat inactivation and by 4MUGS, were identified as carriers also in leukocyte extracts, while heat inactivation alone yielded a small percentage of false positives as determined in repeated analyses in leukocyte extracts. Thus, the 2 test techniques together allow a more accurate estimation of carrier frequency. Nevertheless, if both partners of a couple were found in the heterozygote range by the heat inactivation technique alone they were advised to repeat the test in leukocytes.

Twenty-five microliters of serum or 5 μg protein from leukocyte extracts were incubated with 1.0 mM 4MUGS in 0.1 M citrate-phosphate buffer, pH 4.2, in the presence of 0.5 mg/ml bovine serum albumin in a final volume of 0.25 ml. Enzyme determinations were performed according to Bayleran et al. [1984].

Screening Program

Individuals are referred for the enzyme testing by a coordinator of the Dor Yeshurim organization. They are requested to complete a short questionnaire of previous illness and the use of medication. Each individual is identified by a code number and control number and no names are mentioned. The blood samples are identified by these numbers. Enzyme determinations were performed initially in serum. Results are given by the coordinator only to the couples who are usually to be engaged within a few days and not to individuals. When both partners are in the heterozygote or inconclusive range by the heat inactivation technique they are advised by the coordinator to repeat the test at which time the test is performed in serum and leukocyte extracts. In those instances where the second test indicated that both partners are heterozygotes they were so informed by the coordinator and, if necessary, told by the Rabbi not to proceed with the engagement. Usually this information is dealt only by these instances and no further professional genetic counseling is conveyed. No information is given to individuals not in the engagement process and this is true also when only one partner was found to be a heterozygote and the other a noncarrier; they are just told to go ahead with the wedding. Usually the test is requested just prior to engagement, although recently religious high school students (Yeshiva students) have been screened 1–3 years before engagement and this information is stored in the Dor Yeshurim organization.

RESULTS

The Dor Yeshurim program began in Israel in 1986 and is operated by our center.

Table I demonstrates the development and outcome of this program. Since 1990 the 4MUGS substrate was introduced as the second method for Hex A determination. Our experience indicates that individuals whose enzyme determinations in serum were in the carrier range by the 2 methods together were identified as heterozygotes in leukocytes with no false positives. Nevertheless, individuals in the heterozygote range by the heat inactivation technique alone are also considered carriers and, if necessary, are advised to repeat the test. According to this, the carrier frequency based on those identified by both heat inactivation and 4MUGS together is at least 1:26 and might be somewhat higher, since some carriers might be present in the group of heterozygotes by the heat inactivation method and not detected by 4MUGS. Furthermore, during the 2 years 1990–1991, both partners in 8 couples were identified as heterozygotes in serum and leukocyte extracts. This agrees with the carrier frequency of 1:26, but it should be emphasized that a number of tested individuals are not in the process of engagement (see Materials and Methods); therefore, it is expected that additional carrier couples might be identified in this group and thus once again the carrier frequency might be higher by this calculation.

TABLE I. Screening for the Identification of TSD Carriers in Serum

Year	No. tested	No. carriers (by heat inactivation)[a]	No. carriers (heat inactivation and 4MUGS)[b]
1986	37	4	
1987	463	23	
1988	1645	76	
1989	3523	169	
1990	2703	112	102
1991	2637	140	101

[a] Number of individuals in the heterozygote range by heat inactivation only.
[b] Number of individuals in the heterozygote range identified by heat inactivation and by 4MUGS together (see Materials and Methods section).

DISCUSSION

The importance and success of the screening program for the detection of TSD carriers among Ashkenazi Jews have been recognized not only for its medical and humane achievement but for its cost-effectiveness as well [Kaback et al., 1977; Kaback, 1981]. This program, currently operating in most countries in the Western world with significant Jewish populations, resulted in a 90% reduction of the birth of TSD children in this population in the United States and Canada. Nevertheless, an important part of this population, the ultra Orthodox Jewish community which comprises approximately 10–15% of the Ashkenazi Jews in Israel, do not participate in the programs. Considering the fact that most of the families in this population have at least 7–9 children, including high-risk families for TSD, and the fact that religious restrictions do not permit birth control or prenatal diagnosis, the number of TSD patients in this community remained relatively high, at least in Israel, posing a serious medical and social problem. The program sponsored by Dor Yeshurim changed this picture entirely.

Two crucial requirements guide the operation of this program. The first, test results obtained within a few days of testing. This is to allow for communal engagement customs which usually involve decisions made within a few days and therefore rapid results are obligatory. On the other hand marriages in this community are arranged by the families and thus, the breach of engagement of 2 TSD carriers usually is not very problematic. The second requirement is anonymity of the tested individuals so as to prevent the stigma attached to individuals identified as carriers. Irrational fears of genetic disorders related to carriers are well known in this population. The fact that no names are involved, prompted the support of this program by the spiritual leaders, namely, the important Rabbis from various sectors in the ultra Orthodox community. This was the basis for the success of this program so that hardly any engagement is completed at present prior to the TSD tests.

In all, over 30,000 persons were tested by this program all over the world and 44 carrier couples were identified. Indeed, in Israel no TSD patient has been born to newlywed couples of ultra Orthodox background in recent years. It should be emphasized that this program has also brought about a better understanding of genetic problems in this community and individuals are applying for genetic counseling in increasing numbers.

The frequency of TSD carriers based on either the percentage of heterozygotes in the serum tests by heat inactivation together with the 4MUGS substrate or the number of couples suspected as carriers and retested in leukocytes is at least 1:26 and apparently higher, since not all the tested individuals are yet in engagement process. This is a somewhat higher frequency then estimated by other programs for the general Jewish Ashkenazi population in Israel [Sandhoff et al., 1989]. The higher frequency of the TSD allele in this community stems apparently from the fact that the ultra Orthodox religious Jews in Israel originate mainly from Hungary and Czechoslovakia, where the TSD allele is reported to have the highest frequency [Peterson et al., 1983]. However, it should be emphasized that the need for anonymity precludes in some instances accurate assessments regarding family relationship to be corrected for carrier frequency estimation, though this information in most cases of heterozygous couples is obtained by the coordinator and then corrected appropriately.

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