Carrier Screening for Cystic Fibrosis, Gaucher Disease, and Tay-Sachs Disease in the Ashkenazi Jewish Population

The First 1000 Cases at New York University Medical Center, New York, NY

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Background: By late 1993, the genes for cystic fibrosis and Gaucher disease and the mutations common among Ashkenazi Jews had been identified. In response to these advances, heterozygote screening for cystic fibrosis and Gaucher disease was added to the more than 20-year-old Tay-Sachs disease screening program at New York University Medical Center, New York, NY.

Objective: To review the outcomes from the first 1000 patients screened through this program.

Methods: Patients and their referring physicians were informed about the new carrier tests. At the time of screening, patients could choose their tests (hexosaminidase A by enzyme analysis for Tay-Sachs disease or mutation analysis for cystic fibrosis and Gaucher disease). All partners of Tay-Sachs and cystic fibrosis carriers were tested. Prenatal diagnosis was offered and performed for carrier couples or mixed-marriage couples in whom the Ashkenazi Jewish partner was a carrier of Gaucher disease. Outcomes were measured by: (1) choice of tests, (2) decisions regarding prenatal diagnosis, and (3) phenotypes of children born to patients who underwent screening.

Results: The majority of Ashkenazi Jewish patients chose to have testing for all 3 diseases. If they previously underwent screening for Tay-Sachs disease, then they chose to undergo testing for cystic fibrosis and Gaucher disease. All carrier couples for each of these diseases went on to have prenatal testing. All mixed-marriage couples in whom the Jewish partner was found to be a carrier for Gaucher disease chose to have prenatal diagnosis. One fetus was identified as having cystic fibrosis. Since the program was initiated, no Ashkenazi Jewish baby has been born with any of these diseases at New York University Medical Center.

Conclusions: New tests can be readily incorporated into established heterozygote screening programs. The Ashkenazi Jewish population described herein tends to choose testing for all conditions for which heterozygote screening is available.

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Carrier Screening for Tay-Sachs disease in the Ashkenazi Jewish population has been the paradigm for the development of heterozygote detection programs. Screening for Tay-Sachs disease started in the early 1970s, and to date more than 1 million individuals have been tested. The success of this program has been well documented, and it is highlighted by the reduced incidence of the disorder in the Ashkenazi Jewish population.

For the last few years, the common disease-causing mutations for cystic fibrosis and Gaucher disease have been identified, and mutation frequencies have been determined among Ashkenazi Jewish homozygotes and heterozygotes. Like Tay-Sachs disease in the Ashkenazi Jewish population, cystic fibrosis and Gaucher disease have relatively high carrier frequencies and relatively few mutations that account for a more than 95% detection rate. The success of Tay-Sachs disease carrier programs and the availability of sensitive, relatively low-cost carrier testing for cystic fibrosis and Gaucher disease led to the assumption that screening for these other conditions would be well received in the Ashkenazi Jewish population. As a result, the 20-year-old Tay-Sachs heterozygote detection program at New York University Medical Center, New York, NY, was expanded in January 1994 to include carrier testing for cystic fibrosis and Gaucher disease. This article will review the outcomes from the first 1000 patients screened in this program.
METHODS

The referring obstetricians learned about the modification of the screening program from a newsletter and a brochure, an article in the medical center’s obstetrical journal, an obstetrical grand rounds lecture on carrier testing, and direct contact. Patients learned about the screening program from their obstetricians, during a genetic counseling session for maternal age, reproductive loss, and other related issues, from articles in the Jewish press, and by word of mouth. When patients called for an appointment for screening, they sent a brochure that described the symptoms and natural history of each of the conditions, the autosomal recessive pattern of inheritance, the sensitivity of testing, and the possibility of prenatal diagnosis. On the day of testing, this information was reviewed by a genetic counselor. As part of the genetic counseling, the possibility of being diagnosed as a Gaucher disease homozygote was reviewed. During this time, the patients provided information about their ethnic origin and family history of Tay-Sachs disease, Gaucher disease, and cystic fibrosis. The counselor used this information to determine the patients’ risks of being a carrier for each of the conditions and to recommend tests. Alternatively, information about testing for the various conditions, identification of individual risks, and recommendations about genetic testing were provided during a genetic counseling session that had been initiated for a different indication. In either scenario, after reviewing their screening options with a genetic counselor, the patients provided written consent indicating the diseases for which they wished to have testing and paid for this testing.

Some of the patients who participated in the program were the offspring of mixed marriages. Testing was recommended for all 3 conditions if at least 1 grandparent was Ashkenazi Jewish. Testing was determined by ethnic origin and the existence of a pregnancy. If an Ashkenazi Jewish couple presented prior to pregnancy or early in pregnancy, testing was recommended for only 1 member. If the couple presented at 16 weeks or more in a pregnancy, testing was recommended to both members to have time to perform prenatal diagnosis by amniocentesis. In mixed-marriage couples, testing was recommended for the Ashkenazi Jewish partner first, unless the couple presented at 16 weeks or more into the pregnancy. In that case, testing for Tay-Sachs disease and cystic fibrosis was recommended for both partners. Regardless of pregnancy status, testing for Gaucher disease was offered only to the Ashkenazi Jewish partner because the gene frequency among non-Ashkenazi Jewish persons is low and sensitivity is only around 70% to 80%. For the partners who were not Ashkenazi Jewish, screening tests were recommended that were appropriate to their family history and ethnic origin. Hence, for Sephardic Jews screening was recommended uniformly for β thalassemia and for glucose-6-phosphate dehydrogenase deficiency only if there was a family history of hemolysis.

Carrier testing for cystic fibrosis and Gaucher disease was performed by multiplex polymerase chain reaction followed by allele-specific oligonucleotide hybridization for 32 and 5 mutations, respectively, at Integrated Genetics (now Genzyme Genetics, Framingham, Mass). Carrying testing for Tay-Sachs disease was performed by measuring the percentage of hexosaminidase A activity in serum and leukocytes at Kingsbrook Jewish Medical Center, Brooklyn, NY. Patients were notified of their results by mail unless the laboratory could not complete the test for technical reasons or if the patient was found to be a carrier or have an indeterminant result for Tay-Sachs disease. In such cases, the genetic counselor contacted the patient by telephone. If a carrier was detected, the genetic counselor contacted the patient to request that the partner come in for testing, unless testing was previously performed and documented. Likewise, if an inconclusive result had also been found in the partner, then mutation analysis was offered to resolve these ambiguities. If both members of a couple were identified as carriers, then they were invited for genetic counseling. At this session, a prenatal diagnosis was offered by amniocentesis. Prenatal diagnosis was performed in the same laboratories. Amniocytes were tested for hexosaminidase A deficiency for Tay-Sachs disease and by DNA analysis for the known mutations for cystic fibrosis and Gaucher disease. In mixed-marriage couples, prenatal diagnosis for Gaucher disease by enzyme analysis for β-glucocerebrosidase deficiency was offered if the Ashkenazi Jewish partner was identified as a carrier. These enzyme analyses were performed at Thomas Jefferson University, Philadelphia, Pa. The protocol for expansion of the screening program received approval from the institutional review board at NYU Medical Center.

RESULTS

PATIENT DEMOGRAPHICS

The initial group of 1000 patients included 806 (80.6%) Ashkenazi Jewish patients; 146 (14.6%) white, non-Jewish patients; 30 (3.0%) half-Ashkenazi Jewish patients; and 18 (1.8%) patients of other ethnicity. The majority of patients in the white, non-Jewish group consisted of the partners of Ashkenazi Jewish patients. The half-Ashkenazi Jewish group consisted of patients who by their own admission had only 1 Jewish parent. The group of those of other ethnicity included several Sephardic Jews, patients with only 1 Jewish grandparent, and patients of other ethnic groups. At the time of testing, 800 patients (80%) or their partners were pregnant. By sex, the initial group included 600 females (60%) and 400 males (40%).

TEST SELECTION

In the Ashkenazi population, there was a trimodal distribution in tests chosen, which consisted of testing for Tay-Sachs disease alone (230 patients [23%]), testing for cystic fibrosis and Gaucher disease (260 patients [26%]), or testing for all 3 conditions (420 patients [42%]) (Figure). Patients who selected testing only for cystic fibrosis and Gaucher disease had been screened previously for Tay-Sachs disease. Thus, if the groups are combined, 680 patients (68%) in the Ashkenazi Jewish group underwent testing for all 3 diseases.
CARRIER FREQUENCIES

Of 561 patients tested, the carrier frequency of Tay-Sachs disease in the Ashkenazi Jewish group was 1 in 28. In determining the carrier frequency, we excluded patients who had a family history of any of these diseases. One carrier and 3 patients with inconclusive results were detected in the white, non-Jewish group. In every case, the partners of the patients with inconclusive results were tested and found not to be carriers.

Of 595 patients tested, the carrier frequency of cystic fibrosis in the Ashkenazi Jewish group was 1 in 24. The predominant mutation was W1282X. The cystic fibrosis allele distribution among Ashkenazi Jewish carriers is presented below.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>W1282X</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Delta F508</td>
<td>5 (18)</td>
</tr>
<tr>
<td>G542 X</td>
<td>1 (4)</td>
</tr>
<tr>
<td>3849 + 10-kb C-T</td>
<td>2 (7)</td>
</tr>
<tr>
<td>N1303K</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

One patient with an atypical presentation was diagnosed as having cystic fibrosis. Despite having recurrent pneumonia, the patient was pancreatic sufficient and had normal results of a sweat test. Among the white, non-Jewish group, the carrier rate was 1 in 22 (5 carriers of 112 tested). Of 572 patients tested, the carrier frequency of Gaucher disease in the Ashkenazi Jewish group was 1 in 15. The predominant mutation detected was N370S. The Gaucher disease allele distribution among Ashkenazi Jewish carriers is presented below.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N370S</td>
<td>33 (84)</td>
</tr>
<tr>
<td>R496H</td>
<td>3 (8)</td>
</tr>
<tr>
<td>84gg</td>
<td>3 (8)</td>
</tr>
<tr>
<td>L444P</td>
<td>0 (0)</td>
</tr>
<tr>
<td>IVS2 (+1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

One homozygote who had not been diagnosed previously was identified with this mutation. On recall, he was found to have unexplained episodes of hip pain.

Four double carriers were identified. There was 1 patient who was a carrier for Tay-Sachs disease and Gaucher disease, and 3 patients who were carriers for Tay-Sachs disease and cystic fibrosis.

PRENATAL DIAGNOSIS

All 4 carrier couples identified in this program chose to have prenatal diagnosis by amniocentesis. Among the 2 couples in whom both partners were cystic fibrosis carriers, amniocentesis led to the diagnosis of an affected fetus in 1 case, whereas in the other, a homozygous normal fetus was diagnosed. The pregnancy with the affected fetus was electively terminated. For 1 couple in whom both partners were carriers of Gaucher disease, prenatal diagnosis by amniocentesis led to the diagnosis of an unaffected fetus. Likewise, for 1 couple in whom both partners were carriers of Tay-Sachs disease, prenatal diagnosis by amniocentesis led to the diagnosis of an unaffected fetus. Three pregnancies occurred in mixed-marriage couples in whom the Jewish partner was identified as a carrier of Gaucher disease. In all cases, prenatal diagnosis by enzyme analysis identified an unaffected fetus. Follow-up evaluation of all infants who had prenatal diagnoses confirmed their unaffected status. In addition, a review of this program with the referring obstetricians indicated that no infants had been born at NYU Medical Center with any of these diseases during this period.

COMMENT

This screening program follows the now well-established model in which genetic professionals educate patients so that the patients can make a decision about genetic tests in keeping with their own values. This study demonstrates that when confronted with the possibility of being screened for 3 autosomal recessive conditions, most Ashkenazi Jews choose to do so. Those choosing testing only for Tay-Sachs disease most commonly cited physician recommendation as the reason for their choice. This screening program differs from the Dor Yeshorim approach that has targeted this group of screening tests for people in the orthodox Jewish community. The majority of patients tested at NYU Medical Center are adults for whom a pregnancy was already under way. The population tested in the Dor Yeshorim approach is mainly school-aged adolescents. In the NYU Medical Center program, test results are given to the those who underwent screening and, with their consent, to others. The choice of tests is ultimately at the individual's discretion. Dor Yeshorim does not release test results to individuals, and there is no choice of tests. The differing practices serve the different goals of the 2 programs. The program at NYU Medical Center aims to detect individual carriers and ultimately carrier couples, whereas Dor Yeshorim aims to prevent the marriage of couples in whom both would be carriers for the same disease. In turn, this lessens the risk of conceiving affected fetuses in a community where abortion is generally not acceptable.

Although the exact acceptance rate for heterozygote screening among the target population could not be
determined, 2 factors suggested that it was high. First, during the 2 years covered by this report, there were approximately 4000 deliveries at NYU Medical Center, of which approximately one quarter were to Ashkenazi Jewish patients; hence, even accounting for a high percentage of mixed marriages and a high proportion of orthodox Jews who underwent premarital screening, we would have expected to see at least 1000 patients for screening. Second, no cases of Tay-Sachs disease or cystic fibrosis have been identified among Ashkenazi Jewish infants born at NYU Medical Center in the past 2 years. In addition, the carrier rates and allele distributions were comparable with those that had been reported in previous population-based screening studies of Ashkenazi Jews.4,9,10

The acceptance rate of screening for Gaucher disease in the NYU Medical Center screening program appeared to be quite high. This acceptance was strongly motivated since all patients who were offered prenatal diagnosis for Gaucher disease elected to undergo amniocentesis. Two reasons were commonly cited for choosing screening for Gaucher disease. Some patients indicated a desire to avoid any potential problems in offspring, whereas others indicated the expense of enzyme replacement therapy as a consideration.11 Patients in the screening program understood that Gaucher disease has varying presentations. The majority of people with Gaucher disease are homozygous for the N370S mutation.3 A potential problem arises here because some people with this genotype will present in their childhood years with debilitating hepatosplenomegaly, bone pain, and anemia, whereas others with the same genotype remain relatively asymptomatic with their condition being discovered in late adulthood after some intercurrent illness or as a result of carrier screening. Even siblings with the same genotype can have widely varying phenotypes. This variability in presentation has led many geneticists to move away from offering screening for Gaucher disease. This impression of the correlation between genotype and phenotype was noted in the consensus statement from the National Institutes of Health Technology Assessment Conference on Gaucher Disease12 in February 1995, although the report acknowledged some utility for genetic counseling in using the information on genotype and phenotype. In their published statement, the panelists suggested that pilot studies of carrier screening programs, such as this one, would be useful for determining the acceptability of testing for Gaucher disease. In another article, this suggestion was not included. It should be noted that our program had been under way for more than a year when the National Institutes of Health conference occurred.

The apparent high rate of acceptance of screening for cystic fibrosis was comparable to what was observed among a large prenatal population enrolled in a health maintenance organization, as well as in several screening programs in Europe.14-16 In another American screening program based in a medical genetics center, most (>90%) of the patients were pregnant.20 In contrast, few nonpregnant couples at another university-based center sought screening for cystic fibrosis.21 Thus, it would appear that pregnancy is a major determinant for choosing heterozygote screening. The other major determinant appears to be a medical culture that promotes prevention by screening, whether it is in the context of a health maintenance organization, a national health service, or a well-established precedent based on ethnic background. These factors suggest that barring high costs, new screening tests for autosomal recessive diseases will be used readily by Ashkenazi Jews.

Since screening 1000 patients, we have now modified our screening program by the addition of testing for Canavan disease. This condition in many ways resembles Tay-Sachs disease in presentation and natural history.22 The carrier frequency in the Ashkenazi Jewish population is 1 in 40, and testing for 2 mutations produces more than 95% detection rate.23,24 Screening for 4 conditions (Tay-Sachs disease, Canavan disease, Gaucher disease, and cystic fibrosis) for which the aggregate carrier frequency is 1 in 6 is now standard in our program.

Test development is under way to screen for carriers for other autosomal recessive conditions in the Ashkenazi Jewish population that are associated with mental retardation, birth defects, and/or decreased longevity. These conditions include Fanconi anemia type C, Bloom syndrome, and Niemann-Pick disease type A.25 The carrier frequencies for each of these conditions is approximately 1%, and carriers can be detected by screening for 1 to 4 mutations.26-29 When the genes and common mutations for familial dysautonomia and mucolipidosis IV are identified, these conditions are likely to be candidates for carrier screening.25 Based on our experience with screening for 3 conditions, we anticipate that screening for 7 or even 9 conditions will gain ready acceptance among pregnant Ashkenazi Jews. The advent of new techniques that enable simultaneous detection of many different mutations should aid in preventing higher cost from being a deterrent to screening for multiple conditions.

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