Prenatal Panel Screening Considerations for Non-Neuronopathic Gaucher Disease in the Ashkenazi-Jewish Population

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Abstract

The Ashkenazi-Jewish population is at increased risk for several recessively inherited disorders. While some of the disorders have severe or fatal symptom manifestations, others, such as non-neuronopathic Gaucher disease, do not usually pose a serious, life-threatening illness. Many healthcare centers in Israel offer prenatal panel screening. Controversy exists over the inclusion of Gaucher disease in the panel screening, especially since Gaucher disease screening lacks prognostic reliability. Most screening participants do not discriminate between the specific tests in the panel and are unable to discern between severe, life-threatening diseases and those that are less severe and even treatable. By including screening for Gaucher in the panel screening program, there is risk of a "panel effect," leading to termination of a pregnancy positive for Gaucher disease, without sufficient knowledge and understanding of the disease. Increasing medical and public awareness and knowledge of the disease, its prognosis and treatment options may reduce the rate of under-informed abortions associated with prenatal screening for Gaucher disease.

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Gaucher disease is the most common autosomal recessive disorder in the Ashkenazi-Jewish population [1,2]. The carrier frequency among this population is estimated to be 1 in 15 [3]. Gaucher disease involves a metabolic deficiency in the lysosomal enzyme glucocerebrosidase, resulting in a storage dysfunction and the accumulation of the lipid glucocerebroside in tissues with abundant monocyte/macrophage-derived cells [4] including the spleen, liver, bone marrow and lungs.

While some people with Gaucher disease with the same DNA mutations have a similar clinical course, others with the same mutations have very different clinical manifestations. It is unclear to what extent a person's clinical phenotype or prognosis can be accurately predicted through current mutation analysis. There is a relationship between the type of the mutation and the clinical manifestation, but there is a wide degree of variability among people with the same genotype [5]. Homozygotes for the N370S mutation generally have relatively late onset of the disease, often with mild manifestations. The symptoms associated with these mutations range from an absence of signs and symptoms, as is very common, to severe type 1 Gaucher disease, which is less common. Even for families with multiple affected members, clinical presentation often differs among the family members.

Gaucher disease is manifested in varying degrees of clinical signs and symptoms. There are three types of Gaucher disease. Type 1 Gaucher, which is non-neuronopathic, is the most common, and is genetically linked to the Ashkenazi-Jewish population. Symptoms include enlarged liver and spleen, anemia, reduced platelets, bruising, bleeding, and bone pain and injury. Types 2 and 3 are neuronopathic and are not considered to be associated with Ashkenazi-Jewish ethnicity. The treatment for type 1 Gaucher disease has progressed since the successful development of enzyme replacement therapy. The current drug of choice is a genetically engineered enzyme (Cerezyme™ by Genzyme Corporation, USA). Enzyme replacement therapy can slow and even reverse many of the disease manifestations.

Non-neuronopathic Gaucher disease (type 1) is not usually life-threatening

The current discussion will focus only on type 1 (non-neuronopathic) Gaucher disease as it most applies to the Ashkenazi-Jewish population. Furthermore, among the three types of Gaucher disease, only type 1 fails to meet the requirements for inclusion in screening protocols since it is non-lethal in its nature. Thus, the debate at hand is centered on a genetically inherited disease that manifests in a non-lethal form and is associated with abortion risk when included in prenatal panel screening.

Screening

Community-based screening programs are population-based and have identified thousands of carriers, providing information necessary for obtaining genetic counseling and exploring reproductive options [6]. As such, community-based screening programs have successfully decreased the incidence of infants born with Tay-Sachs disease [6], a genetic disorder lethal in early childhood. Programs have expanded their screening tests to include diseases with relatively high genetic susceptibility. Commercial and academic health centers in the United States and Israel offer screening "panels" that include screening tests for various disorders. Some of the disorders involve fatality in infancy or early childhood, such as Tay Sachs, Canavan disease, familial dysautonomia, and Niemann-Pick disease, while other disorders may lead to death in early or mid-adulthood, such as cystic fibrosis, Fanconi anemia, and Bloom syndrome. Type 1 non-neuronopathic Gaucher disease is an exception in the screening panel since it does not affect the central nervous system and does not usually cause premature death.

The benefits of population screening for Gaucher disease among asymptomatic people have not yet been shown to be necessary or efficacious [2]. In fact, the National Gaucher Committee of the Israel Ministry of Health and the U.S. National Institutes of Health Technology Assessment Panel argue against population screening for Gaucher for various reasons [2,7]. Effective treatment using enzyme replacement therapy is available, but it is costly. Since the Gaucher phenotype is variable, there is a broad range of possible clinical outcomes and screening offers uncertain prognosis [2,7,8]. However, with the wider spectrum of available tests [8], there has been some concern regarding stigma within the Jewish community, especially since a large-scale screening program would identify asymptomatic individuals [7]. Additionally, the NIH Technology Assessment Panel expressed concern regarding the lack of professional and public knowledge of Gaucher disease, an issue that should be addressed through education [2].

Due to the non-lethal nature of the disease and its undeterminable prognosis, the multi-test panel screening kit should not include screening for Gaucher disease

The NIH Panel's concerns regarding education are not without import. In a study of Ashkenazi Jews undergoing genetic screening in New York, education and genetic counseling increased understanding of genetic and disease-related concepts, and minimized anxiety related to screening [9]. In another study of Ashkenazi Jewish couples undergoing prenatal screening, the two most common reasons cited for choosing Gaucher screening were the desire to avoid potential problems in the fetus and financial consideration of treatments [10].

Prenatal screening in Israel

According to the Ministry of Health website [11], 283 people in Israel were reported to have symptomatic Gaucher disease in 2004, although according to the gene frequency it has been estimated that the prevalence of Gaucher disease in Israel should be 2500 [12]. The number reported by the Ministry of Health probably reflects under-reporting and suggests that asymptomatic and mildly affected people escape diagnosis prior to population screening and probably do not require frequent monitoring or "prophylactic" enzyme therapy. In fact, a majority of people diagnosed with type 1 Gaucher disease (such as homozygotes with mutation N370S) have late onset and mild clinical manifestations, especially compared to other, less common mutations (84GG and L444P) that are associated with more serious morbidity and dependence upon long-term treatment [13]. Large-scale population screening in the Ashkenazi population could be deleterious, as it could lead to labeling, stigmatization and discrimination of asymptomatic people. There is also concern that prenatal genetic testing for Gaucher may be a business tactic to attract clients [14].

Prenatal genetic testing is a widespread phenomenon in Israel, but there is no regulation by the Ministry of Health regarding the information provided prior to panel screening or with the revelation of results [14], which may threaten the quality of the information. Some hospital websites advise performing the screening test for Gaucher disease with panel screening [15], while others refrain from doing so, following the recommendation of the Israeli Geneticists Committee not to screen for Gaucher disease [16]. An international, confidential genetic screening system, "Dor Yeshorim," is aimed at preventing the transmission of fatal genetic disorders prevalent in the Jewish community [17]. The program's screening panel includes Tay-Sachs disease, cystic fibrosis, Canavan cisease, familial dysautonomia, Fanconi anemia type C, Bloom syndrome, mucolipidosis type IV, and glycogen storage disorder type I (for Jews of Sephardic origin). Gaucher disease screening was removed from the standard panel due to its non-fatal character as well as the relatively high gene frequency in the Ashkenazi-Jewish population.

The Israeli National Health Law of 1994 defines several prenatal genetic tests to be paid by the state. It includes three categories: amniocentesis during the second trimester for women aged 35 years or older, carrier detection screening for Tay-Sachs, and thalassemia for high risk groups. In addition, there are other prenatal genetic tests not included in the state subsidized medical services that women may choose to have, paying for them privately, out-of-pocket. The price of the additional genetic tests is inexpensive, since they are partially covered by complementary insurance programs and maintain a lower cost when purchased as the commercial panel kits. The number of prenatal genetic tests is constantly increasing, as is the proportion of women using them. Thus, there is concern regarding Israeli overuse of genetic screening as well as the related increasing abortion rates [18]. Furthermore, when exam-

ining non-neuronopathic Gaucher disease specifically, a disease with relatively low disability, the risk of abortion raises serious ethical dilemmas [18].

Ethical considerations and discussion

The NIH Technology Assessment Panel on Gaucher Disease determined that for a specific screening to be appropriate and efficacious, it must meet the following criteria:

- a simple, accurate and relatively inexpensive test to identify carriers at a 95% sensitivity level with high specificity
- a targeted screening population
- a disorder with severe clinical manifestations
- accurate prediction of prognosis and clinical course
- awareness of population needs
- public and professional education regarding the disorder
- informed consent for the screening [2].

Screening for Gaucher disease meets only some of the abovementioned criteria. While the test is simple, accurate and approximately sensitive – 95% for the Ashkenazi Jewish population [3], it does not predict disease prognosis or severity of the clinical manifestations. Gross [18] argues that since Gaucher disease is treatable, the best interests of the fetus precede maternal discretion, and that this interest creates a *prima facie* maternal obligation to maintain the pregnancy, unless maternal health is threatened. Yet, living with Gaucher disease is not without complications and risks for those who are clinically affected.

To date, there has been no proper assessment of the population's needs, attitudes and knowledge of Gaucher disease in Israel. Sagi [19] recommends that a study be conducted prior to offering a population-based screening program for type 1 Gaucher disease to determine if such a program would be beneficial or deleterious. In general, there is a lack of discussion and education regarding the disease in both the professional and public communities in Israel. This lack of education is also reflected in the dearth of genetic counseling prior to screening. Informed consent for panel screening does not usually specify the characteristics and manifestations of each disease, thus leaving Gaucher disease to be included with the other severe and even fatal diseases in the panel. When included in the screening panel, Gaucher disease does not receive its due attention, especially its distinct and contrasting character to the other genetic diseases included in the panel screening.

In contrast to other genetic diseases, Gaucher disease is effectively treated with enzyme replacement therapy, although its cost can be inhibiting. The increased cost may be partially related to the United States Orphan Drug Act, protecting drug development for treatment of rare diseases and decreasing incentive for competition, although some efforts are being invested in developing alternative therapies [18]. The Israeli healthcare system covers the cost of the treatment, given the severity of the disease and the recommendation of a professional committee. Provision of treatment in other countries depends upon insurance and healthcare laws.

Difficulties face many people with Gaucher regarding coverage of the treatment, sufficient dosing, and maintenance of insurance coverage. The costly treatment also raises legitimate questions involving public and private economic considerations for policy makers and healthcare providers especially regarding access to care, social justice, and allocation of resources. There has been some reported success in reducing the dosage and even temporarily withdrawing enzyme replacement treatment in adults with stable Gaucher disease, possibly reducing the prohibitive costs [20].

Comprehensive counseling is crucial for the decision-making process [19]. When counseling a family with a fetus positive for Gaucher disease, caution must be taken not to unnecessarily alarm the family, while providing education and information on the disease, its possible prognosis, and the availability and cost of treatment. Since the Gaucher phenotype is variable, there is a broad range of possible clinical outcomes and no certain prediction of clinical prognosis, confounding genetic counseling and complicating anticipatory guidance.

Currently, Gaucher disease screening lacks prognostic reliability

Conclusions and Recommendations

The debate regarding prenatal Gaucher screening is complex. While type 1 Gaucher disease is non-neuronopathic and usually non-fatal, it includes a range of symptom manifestations – from the more common asymptomatic or mild symptoms to the less common severe target organ involvement that requires extended and costly treatment and management. Population screening is not recommended, according to the NIH Technology Assessment Panel on Gaucher Disease and the Israel Association of Geneticists, as the disease does not meet the population screening criteria. In our opinion therefore, the multi-test panel screening kit should not include screening for Gaucher disease. Commercial availability of multi-screening kits should not set policy for screening programs. Yet, for the couple with a genetic susceptibility for Gaucher disease, especially those at high risk for the mutations associated with severe presentations, specific prenatal screening should be offered. It is important to explain that the genotype/phenotype correlation is imperfect and the prognosis is variable. The screening must be provided with education about the disease and its treatment, genetic counseling, and prenatal options so that the couple may make an informed decision regarding the future of their fetus.

In general, there is a need for the Israeli medical professional community to increase their knowledge and understanding of the disease, its screening, its treatment, and options in order that they may offer their patients accurate and comprehensive infor-

mation. Likewise, there is a need to increase public awareness and knowledge of the disease, to decrease anxiety and minimize under-informed pregnancy terminations of the Gaucher-affected fetus. Additionally, healthcare systems should permit the flexibility of offering specific screening options, according to individual preference. Furthermore, coordinated efforts should be launched between Israeli healthcare systems, healthcare providers, and policy makers to assess population needs and to evaluate screening programs, counseling and education.

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