Screening for Gaucher Disease: New Challenges

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The study by Bronstein et al. [1] in the present issue of *IMAJ* raises some interesting issues concerning genetic screening for rare diseases based on ethnicity and nationality/geography. At the same time, it allows speculation regarding the fundamental purpose of screening for a non-lethal disorder for which there is disease-specific therapy that is safe and effective.

In the current era of heightened awareness of the advantages of "knowing" versus "not knowing," many couples choose to undergo premarital or prenatal screening. The assumption is that they will act upon the results and/or that genetic counseling will be available should the results require it. In Israel, the experience with genetic screening in the ultra-Orthodox community ("*Dor Yesharim*") has had considerable success among individuals of at-risk ethnicities [2]. Since its ultimate goal is to prevent the heartache of devastating and lethal disorders, screening has been integrated into prenatal testing as ethnicity-specific genetic "packages" [3]. At its inception in Israel, the prenatal screening kits for Ashkenazi Jews included Gaucher disease despite the fact that such a screening did not fulfil World Health Organization recommendations, nor is it recommended by the Israel Genetic Association. Yet, there appears to be a continued demand for the Gaucher test [4]. Therefore, if this is the *de facto* status, it behooves experts to ensure that screening maximizes the clinical effectiveness by including mutations that can be considered "severe" or "null" [5] in addition to those most frequently encountered in specific ethnicities [6]. Under both contingencies, there are ramifications for family counseling and prenatal strategies. In the case of identification of a patient by screening for the most common mutations, the consequent step would then allow for an expanded screening among immediate blood relatives. However, in identifying a patient with Gaucher disease carrying both alleles of the most common Ashkenazi Jewish mutation (N370S), there may not necessarily be significant signs or symptoms of the disease [7]. On the other hand, screening for the mutations that have been predictive of severe disease may result in prenatal identification of a fetus with a genotype that is associated with potentially lethal neonatal/infantile types or other severe forms of the disease [8]. Thus, the value of the study by Bronstein and co-workers [1] lies in underscoring this juncture at which mutations should be part of a large-scale screening effort.

The new finding of higher than expected prevalence of the R496H mutation among Israeli Ashkenazi Jewish patients [1], while of epidemiological interest as a (third) common mutation within this population but which had not been delineated as such in an earlier survey [9], does not necessarily support its inclusion in prenatal screening for Gaucher disease. The reason that it might not merit inclusion in a population-screening kit is because there is no association with severe disease manifestations despite the prevalence being relatively high. This is a critical point since other mutations would more adequately meet those criteria. Examples of mutations not included in the population-screening packages but which are predictive of severe disease manifestations are: the V394L mutation that has been reported in patients with seizures or myoclonic features [10], and the D409H mutation that in homozygosity is predictive of the lethal cardiac variant of Gaucher disease [11] but even when paired with another mutation is still considered a severe mutation. The D409H mutation is relatively common among Palestinian Arabs.

The R496H has replaced one of those two mutations in various kits that are now routinely available in Israel. Moreover, the R496H mutation is an ironic choice for inclusion in screening efforts since we know that a mutation in its neighboring amino acid, the R495H mutation, is extant (probably as a cloning artifact) in the cDNA clone from which the first human recombinant enzyme for replacement therapy was developed, further supporting its very mild nature [9]. Thus, R496H, a very mild mutation, which has never been reported in homozygosity, is in our opinion an inappropriate candidate for inclusion in a screening kit for Gaucher disease, despite its putatively greater prevalence among Israeli Ashkenazi Jews. For heightened clinical impact, one of the above mentioned more severe mutations (V394L or D409H) should have been chosen.

Traditional genetic counseling prior to family planning for a person known to be a carrier or for a patient with Gaucher disease would recommend that the partner be tested, and this has typically been performed by using the kit for the more common mutations found among Ashkenazi Jews. We feel the time has come to recommend full gene sequencing of the β-glucocereborsidase gene as opposed to specific (common) mutations since this is becoming more available [12] and affordable. The advantage of full gene

sequencing for a single gene disorder is that it reduces the risk of missing an uncommon but severe mutation. In the future one might recommend whole exome sequencing (i.e., of the protein-coding genes), although admittedly this might engender more information than requisite for an informed decision (informed consent is indeed required) regarding family planning. Clearly this is a challenge that will confront clinicians in the near future as the sum total of informatics derived from sequencing multiplies exponentially.

But, finally, this is no longer the entire story that can be attached to identification of mutations causing Gaucher disease. In the past decade or so, the medical community in general has become aware of the added risk for Parkinson disease not only among patients with Gaucher disease [13] but also among carriers with a single mutation in the β-glucocerebrosidase gene [14]. The presence of a "severe" mutation such as 84GG or L444P in a single copy is associated with a greater risk for an early-onset form of Parkinson disease than the risk associated with "milder" mutations [15]. Thus, the "mild" N370S mutation that had heretofore been considered "neuroprotective" (by definition making the presence of the N370S mutation synonymous with type 1 Gaucher disease), because it has never been identified in patients who suffer from neurological signs (i.e., types 2 and 3 Gaucher disease), is now also recognized as conferring a 2.2-fold increased risk of Parkinson disease [15] among patients and among carriers but the risk is greater for "severe" mutations. This unexpected association between a rare genetic disease and a common neurodegenerative disorder [16] introduces further complexities in the approach of genetic counseling to family planning [17]. While the challenges are clear, the means to address them are not intuitive. Our classic thinking about the clinical ramifications of carrying a single mutation for an autosomal recessive disorder is itself being challenged. The implications of being a carrier of Gaucher disease today may have more devastating implications (i.e., risk for Parkinson disease) than Gaucher disease itself, and this issue is making genetic counseling for Gaucher disease all the more complex.

It is to be hoped that the technology that provides us with pellucid information about our individual genetic codes will also support its clinical explication and application.

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