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Spinal Muscular Atrophy

Committee on Genetics

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ABSTRACT: Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease that results from degeneration of spinal cord motor neurons leading to atrophy of skeletal muscle and overall weakness. In current practice, patients with a family history of SMA are being offered carrier screening for the survival motor neuron gene (*SMN1*) deletion mutations. Recent marketing and public awareness campaigns by laboratories and advocacy organizations are promoting widespread population-based carrier screening for SMA in the prenatal or preconception setting, regardless of family history. However, the American College of Obstetricians and Gynecologists' Committee on Genetics agrees that preconception and prenatal screening for SMA is not recommended in the general population at this time.

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease that results from degeneration of spinal cord motor neurons leading to atrophy of skeletal muscle and overall weakness. The disorder is caused by a mutation in the gene known as the survival motor neuron gene (*SMN1*), which is responsible for the production of a protein essential to motor neurons. There has been recent interest, by both private and professional organizations, in carrier screening for SMA in the general prenatal population (1). This interest has been prompted both by the severity of the disease and relatively high carrier frequency, as well as the advent of improved DNA diagnostic assays for mutations in the disease causing gene (*SMN1*). The genetics of SMA is complex, and because of limitations in the molecular diagnostic assays available, accurate prediction of the phenotype in affected fetuses may be not be possible.

The incidence of SMA is approximately 1 in 10,000 live births and it is reported to be the leading genetic cause of infant death. Carrier frequencies are estimated at 1 in 40 to 1 in 60. There is no effective treatment for the disease. The most severe form, type I (Wernig–Hoffman), has symptomatic onset of the disease before 6 months of age and death from respiratory failure within the first 2 years of life. Type II, the most common form of SMA disease, is of intermediate

severity, with typical onset before 2 years of age. Affected children are able to sit but few are able to stand or walk unaided. Respiratory insufficiency is a frequent cause of death during adolescence; however, the lifespan of patients with SMA type II varies from 2 years to the third decade of life. A milder form, type III (Kugelberg–Welander), has typical symptomatic onset after 18 months of age. However, the symptom profile of affected children is quite variable. They typically reach all major motor milestones, but function ranges from requiring wheelchair assistance in childhood to completely unaided ambulation into adulthood with minor muscular weakness. Many patients have normal life expectancies. There are other forms of SMA-like disorders with similar symptoms as those described previously, but they are linked to genes other than *SMN1*.

Molecular Genetics

There are two nearly identical survival motor neuron genes present in humans, known as *SMN1* and *SMN2*. *SMN1* is considered the active gene for survival motor neuron protein production and more than 98% of patients with SMA have an abnormality in both *SMN1* genes, which can be caused by a deletion (95%), or other mutation. There is generally one, but occasionally two, copies of *SMN1* per chromosome and a variable number of *SMN2* gene copies (ranging from



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zero to three). The *SMN2* gene does not produce much in the way of functional survival motor neuron protein. However, the primary genetic feature, which determines the severity of SMA, appears to be the number of gene copies of *SMN2* in a given individual. Studies have shown that a higher number of *SMN2* copies correlates with generally milder clinical phenotypes. The modulation of clinical severity due to variable copy numbers of *SMN2* is the result of a small amount of full-length survival motor neuron transcripts and the protein generated by *SMN2*. This protein product can partially compensate for the complete absence of protein from the *SMN1* alleles. However, accurate prediction of the SMA phenotype based on *SMN2* copy number is not possible. Although most of the population has one to three copies of *SMN2*, approximately 15% of normal individuals have no *SMN2* gene.

DNA Assay

For diagnosis of SMA, it is sufficient to simply detect the classic *SMN1* deletion using DNA analysis in both *SMN1* alleles. This is approximately 95% sensitive (100% specific) for patients with clinical features suspicious for SMA. However, this approach is not sufficient to identify patients who are heterozygous, or carriers, for the *SMN1* deletion. Carrier testing requires a quantitative polymerase chain reaction assay that provides a measure of *SMN1* copy number. Detection of a single normal copy of *SMN1* would indicate the carrier state.

There are limitations, however, to the use of this assay to determine carrier status. Approximately 3–4% of the general population, having two *SMN1* copies on one chromosome and no copies on the other, will be incorrectly identified as being negative, or not carriers of SMA. These individuals are carriers because one of their chromosomes is missing the *SMN1* allele. Another 2% of the general population has *SMN1* mutations that are not detectable by the polymerase chain reaction method of *SMN1* dosage analysis. Therefore, the counseling of patients who are tested for carrier status must account for the residual risk present when carrier screening assay results are negative, particularly in patients from SMA affected families.

Carrier Screening

In current practice, patients with a family history of SMA are being offered carrier screening for the *SMN1* deletion mutations. Recent marketing and public awareness campaigns by laboratories and advocacy organizations are promoting widespread population-based carrier screening for SMA in the prenatal or preconception setting, regardless of family history. The American College of Medical Genetics has recently recommended offering carrier testing to all couples regardless of race or ethnicity (1). However, to date, no pilot studies have been completed in the United States that would determine best practices for pretest and posttest education and counseling

with specific regard to SMA screening. In addition, there have been no studies to date to determine patient preferences and utility measures that would allow the completion of an analysis of the cost-effectiveness of widespread carrier screening for SMA.

From a public policy perspective, there are generally accepted criteria that a candidate disease should meet before widespread screening is instituted. Briefly, these criteria are: 1) the disease significantly impairs health in the affected offspring; 2) there is a high frequency of carriers in the population to be screened; 3) technically and clinically valid screening methods are available to the population, and screening is cost-effective; 4) testing is voluntary, and informed consent and pretest and posttest counseling are available and effective; 5) fetal testing is available for couples whose screening results are positive and reproductive options are readily available in a time-sensitive manner. In addition to these well-accepted criteria, it is imperative that any screening program be carried out in a manner by which a patient's privacy is protected so that risks of discrimination and stigmatization in the community are minimized. Nevertheless, public awareness campaigns regarding the disease and carrier screening availability will enhance knowledge of SMA and SMA testing in the prenatal population. This may lead to patients requesting SMA carrier testing.

Although SMA does meet some of the criteria cited previously for population-based carrier screening, there are specific areas that have not yet been addressed. In general terms, the question of what threshold for carrier frequency any disease must meet to be considered for widespread screening has never been formally addressed by genetics and public policy professionals. In the case of SMA, carrier frequencies in the general population (1 in 40 to 1 in 60) may be in the range of those found in diseases such as Tay-Sachs (1 in 31), where screening programs are already in place in specific ethnic populations. However, offering SMA carrier screening to the entire prenatal population raises logistic, educational, and counseling issues on a much different scale compared with those screening programs aimed at a small subset of the population. Successful programs for carrier screening in the Eastern European Jewish community that came about with the previously mentioned criteria met and involved a well-informed patient population. In contrast, the well-documented failures of the early sickle cell carrier screening programs highlight the need for appropriate pretest and posttest counseling and for greater attention to the social and clinical needs of the at-risk community. Before panethnic prenatal screening for SMA can be recommended there should be a variety of issues addressed which include, but may not be limited to, critical assessment of pilot screening programs, cost effectiveness analysis, development of appropriate educational materials for both patients and primary obstetrician-gynecologists, and the development of laboratory assay standards and result reporting.

Recommendations

1. Preconception and prenatal screening for SMA is not recommended in the general population at this time.
2. Genetic counseling and SMA carrier screening should be offered to the following patients or couples:
 - a. Those with a family history SMA or SMA-like disease
 - b. Those who request SMA carrier screening and have completed genetic counseling that included discussion of the sensitivity, specificity, and limitations of screening.
3. All identified carriers for SMA should be referred for follow-up genetic counseling for a discussion of risk to the fetus and future pregnancies. Prenatal and preimplantation diagnosis should be discussed, including gamete donations (egg and sperm donors).
4. Patients requesting fetal testing for SMA should be referred to an appropriate provider of prenatal genetic counseling and testing services. If needed, referral for medical and genetic counseling should be made for patients with a fetus found to be affected with SMA.
5. Physicians and counselors involved in carrier screening should make every effort to provide reassurance to patients that the results of screening and diagnostic testing will be held confidentially and that their right to privacy, as with all genetic information, will be respected.

Resources

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