DOI: 10.1097/JPN.0b013e318299c338

CE Continuing Education
J Perinat Neonat Nurs • Volume 27 Number 3, 205–214 • Copyright © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins

The Genetics and Implications of Neuromuscular Diseases in Pregnancy

Kristin L. Frazer, MS, CGC, LGC; Stephanie Porter, MS, WHNP-BC; Christina Goss, MS, WHNP-BC

ABSTRACT

Neuromuscular diseases can have a tremendous impact on pregnant women and affect offspring. Healthcare providers need to have a firm understanding of the genetics involved as well as the potential complications that can arise when treating pregnant women who have been diagnosed with a neuromuscular disease or have an increased risk for delivering an infant affected by one of these disorders. This article provides a comprehensive synopsis of genetics, including the strategies for obtaining a detailed patient and family genetic history through construction of a pedigree, as well as imparting some key knowledge for providing appropriate counseling and treatment to affected individuals and families. It addresses the genetic testing, diagnosis, impact, and medical considerations for both patients and offspring affected by myotonic dystrophy, Duchenne and Becker muscular dystrophies, limb-girdle muscular dystrophy, Charcot-Marie-Tooth disease, and spinal muscular atrophy.

Key Words: genetics, neuromuscular disease, obstetric complications, pregnancy

There are several genetic neuromuscular diseases that can impact pregnant women. The purpose of this article is to ensure proper medical care and management for pregnant women with neuromuscular diseases by understanding the underlying genetics and implications of these conditions. Nurses and other healthcare professionals need to be knowledgeable in genetics to deliver safe and effective care for women undergoing genetic diagnosis, genetic testing, and treatment. Management entails providing education, support, counseling, and appropriate referrals.[1]

GENETIC VERSUS INHERITED

When discussing genetic diseases, it is important to examine the definitions and concepts of common genetic terms. Each individual has approximately 20 000 to 25 000 genes contained in 23 pairs of chromosomes.[2] Chromosome pairs 1 through 22 are found in males and females and are called "autosomes." The 23rd pair, the sex chromosomes, consists of 2 Xs in females and 1 X and 1 Y in males.[1] Only 1 copy of each chromosome is contained in egg cells or sperm cells; therefore, each individual receives 1 copy of DNA from the mother and 1 copy of DNA from the father. Each copy of a gene is called an "allele." If the allele passed from one parent is the same as the allele from the other parent, the individual is homozygous. If the alleles are different, then the individual is heterozygous.[3]

"Inherited" is a term that refers to genes that are passed from one generation to the next. Mutations can be either inherited or de novo (new); therefore, genetic diseases are all caused by mutations in genes that lead to improper cell function, but not all genetic diseases are inherited. An example of this is Duchenne muscular dystrophy (DMD). Only two-thirds of cases of DMD are inherited; the remaining cases are caused by de novo mutations.[3]

FAMILY HISTORY

Reviewing a family history is a key step in identifying genetic conditions affecting an individual or family.[4] Using standard pedigree terminology and constructing a 3-generation pedigree allow providers to build rapport with patients while obtaining information that can be used to help meet the individual's needs.[5] The most common pedigree symbols are shown in Figure 1. Males are designated by squares and are typically placed to

Author Affiliation: University of Tennessee Medical Center, Knoxville, Tennessee.

Disclosure: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Corresponding Author: Kristin L. Frazer, MS, CGC, LGC, University of Tennessee Medical Center, 1924 Alcoa Hwy 6 South, Knoxville, TN 37920 (fraz8525@aol.com).

Submitted for publication: January 31, 2013; accepted for publication: May 1, 2013.

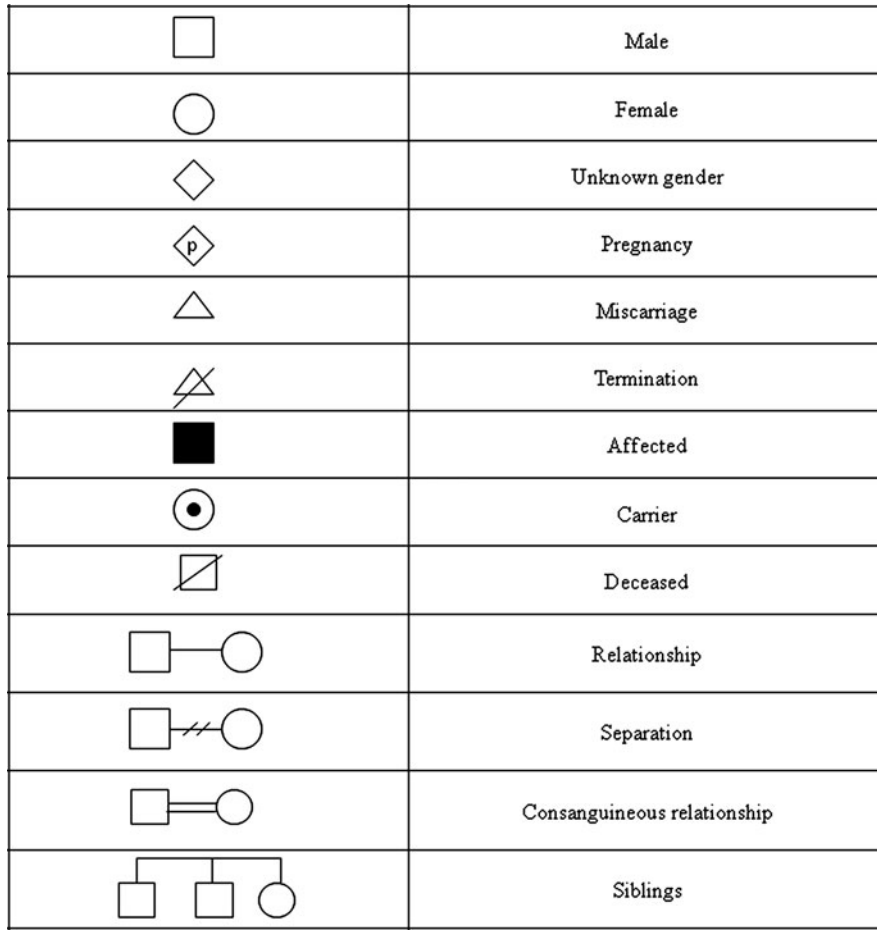

Figure 1. Standard pedigree symbols.

the left of a female partner. Females are designated by circles, and a horizontal line between the square and the circle represents a relationship line. From the relationship line, a vertical line is used to show the next generation.[6] These symbols are used to construct a pedigree that can be used to make a medical diagnosis, establish patterns of inheritance, calculate risks, and aid in making decisions regarding medical management and testing.[6] Constructing a pedigree can be complex and time-consuming. When time is limited, it may be appropriate to have the patient complete a family history intake form such as the one shown in Figure 2.[6]

Using a family history and pedigree is necessary for each patient because it can help identify a typical inheritance pattern of an inherited condition, thus allowing one to make a diagnosis and identify other family members who may be at risk.[3] Following the healthcare provider's discovery of a neuromuscular condition in the family, it is critical to ask follow-up questions to help clarify the diagnosis and ensure that appropriate genetic testing is being ordered.[7] Asking individuals about what testing has already been performed and whether a specific diagnosis has been confirmed in another family member can be helpful.[6] Nurses need to ask the person to describe the condition (problems with muscle weakness, physical movement, or intellectual disability), inquire about age of onset, and make inquiries about alcohol or drug abuse or other medical problems.[6] Nurses and other healthcare providers can use this information to determine possible pregnancy complications, create a healthcare plan, and help make appropriate referrals for further specialty evaluations, such as genetics or neurology. When a personal or family history is elicited in the primary care setting, a referral for preconception counseling may also be warranted.

INHERITANCE PATTERNS

When trying to determine whether a disease is inherited, understanding the ways by which genetic conditions are transmitted is fundamental. Inherited genetic diseases are typically classified in 1 of 3 main categories: single-gene disorders, chromosome abnormalities, or multifactorial disorders.[3] Single-gene disorders involve a gene mutation in 1 or both alleles that causes

Your name: _____ DOB: _____

Have you ever been diagnosed with a genetic condition or birth defect? Yes _____ No _____
If yes, please explain: _____

Do you have any medical conditions such as diabetes, high blood pressure or a thyroid problem?
Yes _____ No _____ If yes, please explain: _____

Have you ever had a child with a major birth defect or health concern? Yes _____ No _____
If yes, please explain: _____

Do you have any muscle weakness and/or problems walking? Yes _____ No _____

Any of your family members or children with muscle weakness and/or problems walking?
Yes _____ No _____ If yes, please include relationship to you: _____

Are these problems related to strength, sensation, coordination, and/or intellect? _____

What parts of the body are affected: feet, hands, upper/lower legs, arms, face? _____

When did these symptoms first begin (age of onset)? _____

Is the condition stable or progressively getting worse? _____

Did you (or the affected person) learn how to walk? Yes _____ No _____ If yes, what age? _____

What testing has been complete? Please circle yes, no, or unsure. If yes, please list results in blank.

Muscle biopsy	Yes	No/Unsure	_____
Nerve conduction studies	Yes	No/Unsure	_____
Metabolic testing	Yes	No/Unsure	_____
MRI of brain/spine	Yes	No/Unsure	_____
Molecular (genetic) testing	Yes	No/Unsure	_____

Any other neurological problems? Please circle yes or no, then list any details in the blanks.

Seizures	Yes	No	_____
Intellectual disability	Yes	No	_____
Vision or hearing loss	Yes	No	_____
Speech problems	Yes	No	_____
Mental illness	Yes	No	_____

Any heart disease or heart conduction defects in the family? Yes _____ No _____
If yes, please explain: _____

Please list any questions or concerns that you have about your family or medical history that have not been covered on this form:
_____

The information I have given on this form is complete and accurate to the best of my knowledge.
Signature: _____ Date: _____

Figure 2. Family history intake form for neuromuscular disease.

a critical error in the function of a specific gene, which can lead to disease. These disorders can be inherited in patterns that follow the rules described by Mendel and are traditionally called autosomal dominant (AD), autosomal recessive (AR), X-linked recessive (XLR), or X-linked dominant.[6]

Autosomal dominant conditions are caused by a mutation in 1 allele of a single gene on an autosome. The pedigree shown in Figure 3 represents common findings in a family with an AD condition. Autosomal dominant conditions affect males and females equally and are seen in each generation. There is a 50% chance with each conception that a parent with a dominant condition could pass on the mutation.[1] Another clue of

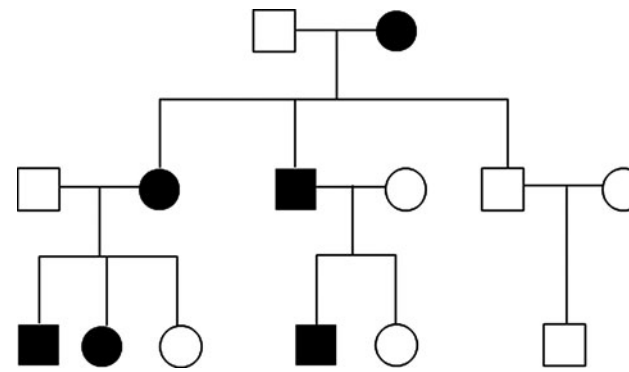

Figure 3. Example of a family history with an autosomal dominant condition. Affected = dark; unaffected = light.

AD inheritance is male-to-male transmission. Since only males pass a Y chromosome on to sons, X-linked inheritance can be ruled out by transmission of a disease from father to son.[3] Sometimes an individual acquires a de novo mutation that can result in an AD condition although there is no family history of the condition. In the case of a de novo mutation, the affected person's siblings would not be at an increased risk for the disease but the affected person would have a 50% risk of passing on the mutation to offspring.[6] Examples of AD neuromuscular conditions include myotonic dystrophy, limb-girdle muscular dystrophy (LGMD), and Charcot-Marie-Tooth disease (CMT).

Autosomal recessive conditions are caused by mutations in both alleles of a gene on an autosome pair. Figure 4 shows a pedigree that represents common findings in a family with an AR condition. Autosomal recessive conditions affect males and females equally and are typically seen only in 1 generation. Typically, siblings can be affected, but parents, offspring, and other family members do not have the condition. Parents of an affected individual are obligate carriers for a mutation but are typically asymptomatic. There is a 25% chance for each sibling to inherit the disease and all of the offspring of an affected individual will be carriers. The disease can also be transmitted if an affected individual has a child with an unaffected partner who is a carrier for the condition. Some types of CMT and spinal muscular atrophy (SMA) are AR.

A third common inheritance pattern evident in family histories is X-linked inheritance. Most of the conditions that are X-linked are recessive (XLR), but X-linked dominant conditions are possible. X-linked refers to a condition that is caused by a gene mutation on the X chromosome.[3] X-linked recessive conditions typically affect males but not females since females have 2 X chromosomes. All the daughters of an affected male will be carriers, but transmission of the disease cannot occur between father and son.[3] Females who carry the mutation have a 50% chance of passing it on. Therefore, sons would have a 50% chance of being affected and daughters would have a 50% chance of being a carrier. Figure 5 shows a pedigree that represents common findings in a family history of an XLR condition. Examples of XLR conditions include DMD and Becker muscular dystrophy (BMD).

GENETIC TESTING AND IMPLICATIONS

In the past, most diagnoses of genetic diseases were based on clinical findings and meeting specific criteria. Recently, molecular testing has become more widely available for hundreds of genetic diseases. Genetic testing can be very confusing. Some people think that a genetic test is a chromosome test, whereas others assume that a genetic test is a direct analysis of DNA. However, genetic tests can include chromosome analysis, molecular DNA sequencing, enzyme analysis, and more. Many individuals think that when genetic testing is performed, the test is for all genetic diseases.[6] Nurses and other healthcare providers need to discuss testing in detail with patients including education regarding how specific tests are performed, the benefits and limitations of each test, and the concept of residual risk.

Genetic testing serves many different purposes. Besides making a diagnosis for an individual, genetic testing can be used to predict the risk for the offspring to inherit a specific condition.[1] Prenatal diagnosis or

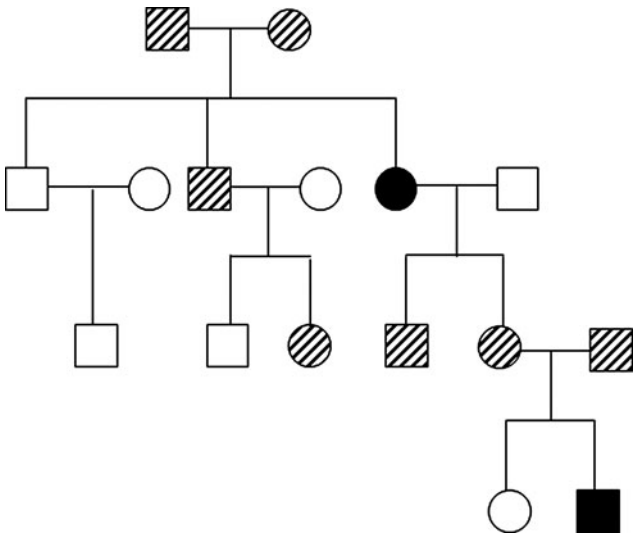

Figure 4. Example of a family history with an autosomal recessive condition. Affected = dark; unaffected = light, carrier = striped.

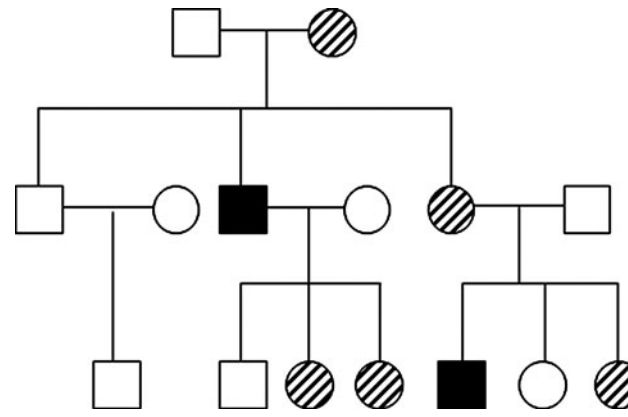

Figure 5. Example of a family history with an X-linked recessive condition. Affected = dark; unaffected = light; carrier = striped.

preimplantation genetic diagnosis may be considered if a parent has had molecular testing in which a gene mutation has been identified.[7] For individuals with a genetic disease, or a family history of a specific genetic disease, availability of testing for preimplantation genetic diagnosis or prenatal diagnosis may be of great consequence in family planning decisions. Some couples may desire prenatal testing to make decisions about termination of an affected pregnancy. Other couples may want to pursue prenatal genetic testing to have additional time during the course of pregnancy to prepare for having a child with special needs. This enables parents to research more about the condition prior to the infant's arrival and allows time to better prepare siblings and other family members for the birth of an affected child. In addition, prenatal diagnosis may alter the delivery plan for the pregnancy, such as the mode of delivery and/or the location of delivery to ensure the proper neonatal care following delivery.[1]

SPECIFIC NEUROMUSCULAR DISEASES

Neuromuscular disorders lead to several dilemmas and concerns for affected women of childbearing age and the healthcare providers who provide treatment. In addition to the hereditary risks of the underlying genetic diseases, there are concerns such as decreased fertility, worsening of maternal symptoms during pregnancy, and an increased likelihood of miscarriage, preterm labor, and need for delivery intervention, such as forceps- or vacuum-assisted vaginal delivery or cesarean delivery.[8,9] Hereditary neuromuscular disorders can become more symptomatic for women during pregnancy, may require use of medications during pregnancy that increase risk for birth defects and pregnancy complications, and call for specialized medical and pregnancy management, such as antepartum anesthesia consultation, to determine whether a patient's delivery location requires anesthesia services on a 24-hour basis.[10,11] Despite the various potential issues surrounding pregnant women with neuromuscular disorders, serious complications are rare during pregnancy.[10] Although women with neuromuscular disorders who become pregnant can experience long-lasting, negative effects on their disease states, many achieve successful pregnancies without major complications.[9]

Myotonic dystrophy

Myotonic dystrophy is the most common inherited muscular dystrophy that affects adults, including women of childbearing age.[10] It is estimated that about 1 in 8000 adults have myotonic dystrophy, an AD condition that is characterized by myotonia, muscular dysfunction (including weakness, pain, and stiffness), cataracts, cardiac conduction defects, type 2 diabetes, and testicular failure.[12,13] Myotonic dystrophy is divided into 2 types as they are caused by 2 different gene mutations. The proportion of individuals with type 1 versus those with type 2 is unknown.[12] Both types are caused when a specific sequence of 3 nucleotides is repeated a number of times (called a trinucleotide or triplet repeat), which expands to an increased number of repeats over a certain threshold, leading to adverse effects of gene function resulting in disease. However, type 1 is associated with anticipation, which is generally seen when the condition is inherited from the mother.[13] Anticipation refers to the trinucleotide repeat expanding when it is passed from one generation to the next, which causes the symptoms of disease to become more severe and to appear at an earlier age.[9] Individuals with myotonic dystrophy inherit the condition from an affected parent since the de novo mutation rate is close to zero for this condition. Parents may be undiagnosed because they have a mild form or because they have been misdiagnosed with fibromyalgia, rheumatoid arthritis, inflammatory myopathy, or an atypical motor neuron disease.[12]

Myotonic dystrophy type 1 is typically divided into 3 subtypes that include mild (late-adult onset), classic, or congenital.[10] The subtypes of myotonic dystrophy type 1 are based on age of onset but are also typically related to the size of the triplet expansion. Individuals with mild type 1 typically have 50 to 150 repeats and start to show symptoms between 20 and 70 years of age. Those with classic type 1 have between 100 and 1000 repeats and begin showing symptoms between 10 and 30 years of age. Congenital myotonic dystrophy type 1 is usually present at birth and is related to an expansion of greater than 2000 repeats. It is characterized by severe hypotonia and generalized weakness at birth.[13]

The congenital form of myotonic dystrophy is virtually always caused by anticipation in the gene inherited from the mother.[14] A female who is asymptomatic or has minimal disease has less than a 5% chance of having an infant with the congenital form. If she has moderate disease symptoms prior to pregnancy, the risk of having a congenitally affected infant is 10% to 30%, and if she has delivered an infant from a previous pregnancy that was born congenitally affected, the recurrence risk is 40%.[4] Congenital myotonic dystrophy results in either neonatal death from respiratory insufficiency or severe childhood disease that is associated with severe physical handicaps and intellectual disability in 50% to 60% of survivors.[4,13] The congenital form is often associated with abnormal ultrasound findings that include clubfeet and polyhydramnios.[15]

Women who have been diagnosed with type 1 have an increased risk for an ectopic pregnancy, late

spontaneous abortion, preterm labor, preeclampsia, polyhydramnios, a prolonged labor with increased rate of cesarean delivery, placenta previa, and postpartum hemorrhage.[8] In women with myotonic dystrophy type 1 and clinical signs of the disease at pregnancy onset, the preterm delivery rate can be as high as 50%. The rate of perinatal loss is almost 10 times higher in women diagnosed with myotonic dystrophy type 1 than in women in the general population.[14] This increased risk for pregnancy complications and perinatal loss seems to be at least partially related to the fetal status.[8] Affected fetuses tend to swallow less and have reduced fetal movement, which is associated with the development of polyhydramnios and preterm labor.[8] Neonates with myotonic dystrophy type 1 can have respiratory problems following birth, leading to an increased mortality rate.[15]

There are many important considerations when providing care for women with type 1 during the perinatal period. These women frequently experience issues during all stages of labor because of the uterine muscle abnormality associated with the condition.[8,10] For those who require tocolytic therapy for threatened preterm labor, the use of β-adrenergic antagonists is contraindicated secondary to that class's propensity for worsening myotonia.[10] With its neuromuscular blocking action, magnesium sulfate infusion must be avoided to prevent worsening muscle weakness and respiratory compromise.[8] Caregivers must also be aware that general anesthesia and narcotics need to be avoided if at all possible. If necessary, these women will certainly require lower doses of narcotics during the delivery process to reduce the risk of respiratory suppression. A greater potential for anesthesia complications, such as prolonged ventilation, atelectasis, and pneumonia, exists throughout the perinatal period.[10,13] Increased respiratory monitoring and encouragement of incentive spirometry use are vital during the postnatal period. These women are also at risk for worsening cardiac function due to conduction defects and arrhythmias.[13] Hence, anesthesia consultation prior to delivery can help ensure proper management during and following delivery.

Myotonic dystrophy type 2 has not been associated with developmental abnormalities or severe disease in childhood. Unlike type 1, there is not a congenital form of type 2. Consequently, pregnancy and delivery complications related to the fetus have not been reported in women with type 2. However, like type 1, preterm labor can represent a potential concern, with a significantly higher preterm delivery rate for pregnancies in patients who are symptomatic. These women possess an increased risk of early pregnancy loss as well.[16] Pregnancy can pose other adverse effects on women affected by type 2. An unexplained shift toward an earlier age of symptom onset in women exists for those who have given birth. If symptoms begin prior to pregnancy and deteriorate during pregnancy, or if the first symptoms of myotonic dystrophy occur during pregnancy, there is usually improvement after delivery, but symptoms reoccur in subsequent pregnancies.

In addition to increased surveillance during pregnancy for the potential obstetric complications already discussed, a referral for consultation with a cardiologist is appropriate for women with myotonic dystrophy. Both types of myotonic dystrophy are associated with cardiac conduction defects and arrhythmias and also have been associated with an increased risk for cardiomyopathy and sudden death.[13]

Duchenne muscular dystrophy/Becker muscular dystrophy

Probably the most well-recognized muscular dystrophies are the XLR dystrophinopathies called "Duchenne muscular dystrophy" and BMD. These conditions are suspected when males have a gradual onset of proximal weakness in childhood.[7] Although these conditions are caused by changes in the same gene, they are still considered separate conditions because the clinical manifestations and age of onset differ. Duchenne muscular dystrophy occurs in approximately 1 in 3500 live male births, whereas BMD occurs less frequently in about 1 in 18,500 male births.[17] The gene involved in these conditions is responsible for producing a protein called "dystrophin," which is absent in DMD and is reduced or has an altered structure in BMD.[4] These dystrophinopathies can be diagnosed by DNA testing, but a negative test result does not exclude the diagnosis. Muscle biopsy can be used for diagnosis in a case in which the DNA test is negative.[18]

Duchenne muscular dystrophy is characterized by normal development during the first year or two of life, with the development of muscle weakness starting between 3 and 5 years of age. Affected males usually begin to have difficulty climbing stairs and rising from a sitting position without additional support. The progression of the disease is relentless and the affected male is usually confined to a wheelchair by the age of 12 years. An affected individual is unlikely to survive much past the age of 20 years. Most patients with DMD die of respiratory failure or of cardiac failure because of the progressive deterioration of the myocardial muscle.[3] Through molecular testing and muscle biopsy, it has been determined that about one-third of cases of DMD are due to de novo mutations and two-thirds of cases are from carrier mothers. The majority of females who carry a mutation in the dystrophin

gene have no clinical symptoms, but up to 8% of female carriers can have significant muscle weakness.[3]

Molecular testing can identify deletions or duplications in 60% to 70% of males with DMD and can find other mutations through sequencing in 20% to 25% of those affected.[19] Therefore, there are about 5% to 10% of affected males who will have a negative genetic test result. This can lead to complications in the testing of other at-risk family members. If an affected male does not have a detectable mutation, a negative test result for family members would not rule out the possibility of being a carrier or of having an affected child, and prenatal diagnosis would not be an option. If a mutation has been detected in a male family member, females can undergo carrier testing and prenatal diagnosis if desired. Since female carriers are typically asymptomatic and the disease is associated with normal development in infancy, there are no apparent increased risks for fetal abnormalities or pregnancy complications for the mother.

Becker muscular dystrophy is typically characterized by progressive muscle weakness starting in the adolescent years. Many males with BMD remain ambulatory into adult life but have increasing disability. Because affected males survive into adulthood, many of them reproduce, which means that all of their daughters will be obligate carriers and will have a 50% chance of having an affected son. Females with affected fathers must understand that they are carriers for BMD and carrier testing is not necessary. Carrier testing can actually be harmful by causing false reassurance if the mutation is undetectable or if their creatine kinase levels are within reference ranges.[4] Becker muscular dystrophy can have significant variability but overall, it is much milder than DMD. The chance of having a son with BMD caused by a de novo mutation is only about 10%; therefore, 90% of males affected with BMD have a carrier mother.[3]

Limb-girdle muscular dystrophy

"Limb-girdle muscular dystrophy" is a term used to describe several types of muscular dystrophies that are commonly characterized by a limb-girdle pattern of muscle weakness without facial involvement. Limb-girdle muscular dystrophies are caused by various proteins with different functions.[18] The symptoms of most LGMDs are typically limited to skeletal muscle. Most affected individuals show progressive weakness and muscle wasting in the musculature of the limbs, with proximal muscles being more affected than distal muscles.[9,20] Most LGMDs are AR, but a few rare types are AD. If symptoms occur at an early age and are severe, LGMD can resemble DMD. It is critical to eliminate the dystrophinopathies when a young male presents with symptoms of muscular dystrophy. The diagnosis of LGMD in any female who appears to have classic symptoms of DMD needs to be considered.[4]

Limb-girdle muscular dystrophies are most commonly seen in later childhood to early adulthood. They are typically diagnosed by the combination of clinical findings, classic dystrophic changes on muscle biopsy, biochemical testing on muscle biopsy, and/or molecular genetic testing.[20] The muscle biopsy is used to find a reduction in the causative protein and then appropriate genetic testing can be used to analyze the likely contributing gene to establish a genetic diagnosis.[18] Molecular genetic testing is clinically available for most gene mutations that have been identified to cause LGMD; however, there are still many types of LGMD that have not been linked to a specific mutation. It is estimated that about 50% of affected individuals do not have a molecular diagnosis.[20]

Because of the lack of diagnostic specificity and the various types of LGMD, the prevalence of these disorders is difficult to determine; estimates range from 1 in 14,500 to less than 1 in 120,000 affected.[20] Most individuals diagnosed with LGMD represent the only case of the disease in the family. Families can be counseled that typically these conditions are rare recessive conditions and that the only considerable risk for recurrence is for the affected relative's siblings.[20] Parents of the affected person are considered obligate carriers, are asymptomatic, and have a 25% chance with each pregnancy that they conceive together of having an affected child. If the affected person has had molecular genetic testing and has a detectable mutation, the parents can elect to have prenatal diagnosis during pregnancy or they can pursue preimplantation genetic diagnosis. The variation of these conditions can be seen within the family, meaning that the age of onset and/or the progression of the disease cannot be predicted for affected siblings.[20]

There are a few types of LGMD that follow an AD inheritance pattern. In these cases, the offspring of an affected parent have a 50% chance of inheriting LGMD. Some family histories appear negative for the disorder due to failure to recognize this disorder in a family member or misdiagnosis of a family member. It is also possible that an affected parent died at an early age before the onset of symptoms or that the parent has not yet been diagnosed because of the potential late onset of the condition. The result of these complications makes determining the rate of de novo mutations for LGMD impossible.[20]

Unlike the other dystrophinopathies, LGMDs can affect women of childbearing age. There are no congenital forms of LGMD, so the only increased risk of obstetrical complications is associated with the affected mother's underlying condition. In one study, more than 50% of women with LGMD reported experiencing

worsening of weakness during pregnancy. The worsening was most likely weight related but generally did not improve after delivery. All of the women in the study attributed this worsening to the expected progression of the disease and still reported a positive attitude toward pregnancy. These women emphasized the value of carrying a child and starting a family despite their physical disabilities or the need for assistance to care for their infants.[9,10,21] Women who have been diagnosed with an LGMD are often concerned about the risk of offspring inheriting the condition. Most LGMDs are recessive and the carrier frequency in the general population is low (estimated to be <1 in 150); therefore, the risk for an affected parent to have a child with the same condition is much less than 1% (~1 in 300 or less). Carrier testing for unrelated partners is unavailable because of the heterogeneity of the disease.[20]

Charcot-Marie Tooth

Charcot-Marie Tooth is actually a group of hereditary diseases that are characterized by both motor and sensory neuropathies. These conditions affect approximately 1 in 2500 individuals, which means that they are among the most common hereditary neuromuscular disorders.[10] This group of disorders can be inherited in an AD, AR, or X-linked pattern, with AD inheritance being the most common inheritance of CMT. There are several types of CMT that are typically differentiated by inheritance patterns and/or by nerve conduction studies.[4] Charcot-Marie Tooth can be distinguished from other hereditary neuropathies such as hereditary sensory and autonomic neuropathies and hereditary motor neuropathies by the level of sensory involvement. Patients with CMT always have sensory involvement, which is more severe in hereditary sensory and autonomic neuropathies and absent in hereditary motor neuropathies.[18]

Charcot-Marie Tooth is often diagnosed clinically. Typical evaluations for inherited neuropathies include a comprehensive neurologic examination, nerve conduction studies, and a thorough review of the family history.[7] Charcot-Marie Tooth type 1 is the most common type of CMT, which is characterized by delayed nerve conduction and affects up to 50% of individuals with CMT. It is generally inherited in an AD pattern, but X-linked inheritance has been reported in some families. This is sometimes abbreviated as CMTX and appears in up to 15% of individuals with type 1. In the past, there were a few families believed to exhibit an AR inheritance pattern; however, in most of these families, the condition is now believed to be caused from either mosaicism in a parent (including germ line mosaicism) or undetected disease in a parent.[4,22] Charcot-Marie Tooth type 2 is also typically inherited in a dominant manner, but it is associated with normal nerve conduction and can be milder than type 1.[4] It is seen in 10% to 15% of individuals with CMT.[22] There still appears to be a type of CMT that is inherited in an AR manner but this is rare. Family histories may appear negative, but this can be secondary to undiagnosed CMT or a misdiagnosis in a family member, early death of an affected parent prior to onset or diagnosis, or late onset in an affected parent.[22]

Charcot-Marie Tooth usually presents in childhood or early adulthood with progressive distal weakness and distal muscle wasting. Most individuals are diagnosed prior to 30 years of age.[3] The age of onset, severity of symptoms, and progression of the disease vary significantly between individuals, even within an affected family. Symptoms of CMT typically start in childhood with slow progressive weakness and then atrophy of the distal leg muscles. This usually leads to an abnormal gait, dropped foot, and foot deformities. Affected individuals usually experience loss of balance and require aids such as special foot and ankle braces or canes, but less that 5% lose the ability to walk.[22] Weakness in the hand muscles and hand deformities typically occur later in the course of the disease.[3]

When taking care of women with CMT, certain considerations exist. First, healthcare providers need to understand the potential effects of the condition on the pregnancy course as well as the effects of pregnancy on the mother's condition. Until recently, CMT was believed to have no significant impact on pregnancy, delivery, or the newborn.[23,24] However, more recent studies have demonstrated relevant pregnancy and delivery complications, and there are increased maternal risks as well.[8,9,25] Pregnancies of mothers with CMT are 2 times more likely to have presentation anomalies and are twice as likely to require operative deliveries, such as forceps- or vacuum-assisted vaginal deliveries or cesarean deliveries. It has been speculated that the increased risk for breech presentation or abnormal cephalic presentation that predisposes these patients to require an operative delivery manifests from the maternal condition itself or as the result of decreased fetal motility.[8,25] Mothers with CMT are twice as likely to encounter severe postpartum bleeding, possibly related to uterine atony caused by neuropathy of uterine adrenergic nerves.[9,25] Thus, immediate treatment of a postpartum hemorrhage needs to be anticipated. If a woman was diagnosed with CMT in early childhood, there is a 50% risk of deterioration of the disease during pregnancy. It is speculated that endoneurial edema and the pressure effects from the gravid uterus contribute to the worsening of disease symptoms during pregnancy.[10] About one-third of the women with exacerbations or

deterioration reported improvement after delivery, but the other two-thirds experienced progressive worsening of symptoms in the postnatal period.[23] Women who experienced exacerbations in their first pregnancies generally had a high risk of exacerbations in subsequent pregnancies. Women with adult-onset CMT, interestingly, did not typically report any worsening of symptoms during pregnancy.[9] Fortunately, affected infants are not expected to have any symptoms at birth.[8]

Another factor to consider when caring for a female with CMT is the inheritance of the condition and how that might impact the family. Since most individuals have a dominant form of the condition, the risk for offspring to be affected is up to 50%. However, for patients who do not have a family history of CMT and the inheritance pattern remains unclear, there are no empiric data regarding the recurrence risk for offspring. The availability of molecular testing for the most common gene mutations detected in CMT can help determine recurrence risk, but if a mutation is not detected, a recurrence risk cannot be predicted.[22] In these cases, the recurrence risk could be as high as 50%. Discussing these risks with women is vital because up to 36% of individuals with CMT rate their level of disability as high and may choose not to have children.[26] Nurses need to acknowledge the difficulty of accepting an unplanned pregnancy and should consider the emotional impact of pregnancy as well as the physical impact that the pregnancy poses on the mother's health.

Spinal muscular atrophy

Spinal muscular atrophy describes a group of motor neuron disorders that are caused by the degeneration and death of lower motor neurons in the anterior horn of the spinal cord and brain stem. Spinal muscular atrophy is AR and typically affects infants and children but can occur in adults.[7] It is characterized by progressive muscle weakness, joint contractures, scoliosis, and a history of motor difficulties or failure to meet developmental milestones, and it is caused by various mutations in the *SMN1* gene that cover a continuum without distinct molecular changes to separate subtypes.[27] Thus, subtypes are typically grouped by age of onset and maximum function achieved. Considering subtypes is useful for prognosis and management of the disorder, as well as thinking about the potential for pregnancy-related concerns. Regarding pregnancy, the 2 main issues to consider include the effects of a pregnancy on a woman affected with SMA as well as the potential complications seen in a pregnancy when the fetus inherits the disease.

Typically, SMA is divided into 3 to 5 different subtypes. SMA I is commonly associated with onset of the condition prior to birth up to 6 months of age and is related to poor muscle tone, weakness, and mild to severe contractures. SMA I can be further divided into 2 different subtypes, SMA 0 and SMA I, with SMA 0 being the most severe. Spinal muscular atrophy 0 can be related to arthrogryposis multiplex congenital, weakness at birth, and/or respiratory failure, with a life span of between 2 and 6 months. In infants with SMA I, onset is prior to 6 months of age and death typically occurs before 2 years of age. Individuals with SMA II (also called "chronic SMA") are typically diagnosed between 6 and 12 months of age, are nonambulatory, and have low muscle tone and progressive weakness. Seventy percent of patients with SMA II survive past 25 years of age. SMA III is frequently diagnosed in childhood, but after 10 months of age, and they have a normal life span. Individuals with SMA III can usually walk but experience frequent falls and trouble climbing stairs by 2 to 3 years of age. Spinal muscular atrophy III is also sometimes divided into 2 subtypes, SMA III and SMA IV. Spinal muscular atrophy IV is the adult onset form of the disease.[27]

Spinal muscular atrophy is one of the more rare neuromuscular diseases that can be seen in women of childbearing age, with a prevalence in the general population of approximately 1 in 10,000.[6] Pregnant women with SMA have had successful pregnancy outcomes, although often these women are discouraged from getting pregnant.[10] About 80% of women with SMA experience complications during pregnancy, which include preterm labor and worsening of disease symptoms.[8] For women with SMA who experience preterm labor, the same precautions need to be executed as previously discussed for women with myotonic dystrophy. Exacerbations of muscle weakness occurred in two-thirds of pregnant patients with SMA and seemed to be persistent in more than half of these women following delivery.[9]

Both delivery and anesthesia decisions are often impacted by whether leg contractures, scoliosis, or spinal fixation that women can possess with severe SMA are present. At the time of delivery, women with SMA have potential for respiratory complications, airway difficulties, and concerns related to the presence of scoliosis and spinal column deformities. Careful planning is necessary prior to delivery to reduce maternal risks. Cesarean delivery is the usual mode of delivery, but less affected patients can deliver vaginally. For women who are severely affected by SMA, have spinal column deformities, and require cesarean delivery, anesthesia options can be complexing.

SUMMARY

Many neuromuscular diseases affect women of childbearing age. A significant number of these genetic

conditions can be associated with increased risks for pregnancy complications. Understanding the genetics relevant to these conditions including the inheritance patterns, frequency of the diseases, risks for offspring to be affected, and the availability of genetic testing or prenatal diagnosis ensures effective medical care.

References

1. Lewis JA. *Genetic Issues for Perinatal Nurses*. 3rd ed. White Plains, NY: March of Dimes Foundation; 2010.
2. National Human Genome Research Institute. An overview of the human genome project. http://www.genome.gov/12011238. Accessed December 23, 2012.
3. Nussbaum RL, McInnes RR, Willard HF. *Thompson & Thompson Genetics in Medicine*. 6th ed. Philadelphia, PA: WB Saunders Company; 2001.
4. Harper PS. *Practical Genetic Counselling*. London, England: Hodder Arnold; 2004.
5. Baker DL, Schuette JL, Uhlmann WR. *A Guide to Genetic Counseling*. New York, NY: Wiley-Liss; 1998.
6. Bennett RL. *The Practical Guide to the Genetic Family History*. New York, NY: Wiley-Liss; 1999.
7. Krajewski KM, Shy ME. Genetic testing in neuromuscular disease. *Neurol Clin*. 2004;22:481–508.
8. Argov Z, DeVisser M. What we do not know about pregnancy in hereditary neuromuscular disorders. *Neuromuscular Disord*. 2009;19:675–679.
9. Guidon AC, Massey EW. Neuromuscular disorders in pregnancy. *Neurol Clin*. 2012;30:889–911.
10. Sax TW, Rosenbaum RB. Neuromuscular disorders in pregnancy. *Muscle Nerve*. 2006;34(5):559–571.
11. Riley LE, Stark AR. *Guidelines for Perinatal Care*. 7th ed. Elk Grove, IL: American Academy of Pediatrics; 2012.
12. Dalton JC, Ranum LP, Day JW. Myotonic dystrophy type 2. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews* [Internet]. Seattle, WA: University of Washington; 1993. http://www.ncbi.nlm.nih.gov/books/NBK1466/. Updated April 23, 2007. Accessed 2012.
13. Bird TD. Myotonic dystrophy type 1. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews* [Internet]. Seattle, WA: University of Washington; 1993. http://www.ncbi.nlm.nih.gov/books/NBK1165/. Updated February 8, 2011. Accessed 2012.
14. Rudnik-Schoneborn S, Nicholson GA, Morgan G, Rohrig D, Zerres K. Different patterns of obstetric complications in myotonic dystrophy in relation to the disease status of the fetus. *Am J Med Genet*. 1998;80:314–321.
15. Zaki M, Boyd PA, Impey L, Roberts A, Chamberlain P. Congenital myotonic dystrophy: prenatal ultrasound findings and pregnancy outcome. *Ultrasound Obstet Gynecol*. 2007;29(3):284–288.
16. Rudnik-Schoneborn S, Schneider-Gold C, Raabe U, Kress W, Zerres K, Schoser BG. Outcome and effect of pregnancy in myotonic dystrophy type 2. *Neurology*. 2006;66:579–580.
17. Emery AE. Population frequencies of inherited neuromuscular diseases: a world survey. *Neuromuscul Disord*. 1991;1:19–29.
18. Reilly MM, Hanna MG. Genetic neuromuscular disease. *J Neurol Neurosurg Psychiatry*. 2002;73:ii12–ii21.
19. Darras BT, Miller DT, Urion DK. Dystrophinopathies. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews* [Internet]. Seattle, WA: University of Washington; 1993. http://www.ncbi.nlm.nih.gov/books/NBK1119/. Accessed 2012. Updated November 23, 2011.
20. Pegoraro E, Hoffman EP. Limb-girdle muscular dystrophy overview. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews* [Internet]. Seattle, WA: University of Washington; 1993. http://www.ncbi.nlm.nih.gov/books/NBK1408/. Updated August 30, 2012. Accessed 2012.
21. Rudnik-Schoneborn S, Glauner B, Rohrig D. Obstetric aspects in women with facioscapulohumeral muscular dystrophy, limb-girdle muscular dystrophy, and congenital myopathies. *Arc Neurol*. 1997;54(7):888.
22. Bird TD. Charcot-Marie Tooth hereditary neuropathy overview. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews* [Internet]. Seattle, WA: University of Washington; 1993. http://www.ncbi.nlm.nih.gov/books/NBK1358/. Updated September 27, 2012. Accessed 2012.
23. Rudnik-Schoneborn S, Rohrig D, Nicholson G, Zerres K. Pregnancy and delivery in Charcot-Marie Tooth disease type 1. *Neurology*. 1993;43:2011–2016.
24. Shy ME, Garbern JY, Kamholz J. Hereditary motor and sensory neuropathies: a biological perspective. *Lancet Neurol*. 2002;1:110–118.
25. Hoff JM, Gilhus NE, Daltveit AK. Pregnancies and deliveries in patients with Charcot-Marie Tooth disease. *Neurology*. 2005;64:459–462.
26. Pfeiffer G, Wicklein EM, Ratusinski T, Schmitt L, Kunze K. Disability and quality of life in Charcot-Marie Tooth disease type 1. *J Neurol Neurosurg Psychiatry*. 2001;70:548–550.
27. Prior TW, Russman BS. Spinal muscular atrophy. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews* [Internet]. Seattle, WA: University of Washington; 1993. http://www.ncbi.nlm.nih.gov/books/NBK1352/. Updated January 27, 2011. Accessed 2012.