Malignant hyperthermia (MH) is a genetic condition where individuals are more likely to have severe reactions to specific types of medications. For this reason, it is also called "malignant hyperthermia susceptibility" (MHS). The types of medications people may have reactions to include certain gas anesthetics (used to block pain) and the muscle relaxant succinylcholine (used for temporary paralysis during surgery or other procedures). If exposed to one of these medications, individuals with MHS are at risk to develop a variety of symptoms that include increased levels of acid in the body (which can cause increased or rapid heart rate, or possibly cardiac arrest), increased levels of carbon dioxide in the body (which can cause abnormal breathing), muscle rigidity, breakdown of muscle fibers with leakage into the blood and urine (rhabdomyolysis, which can be harmful to the kidneys), and hyperthermia (abnormally high body temperature). Those with MHS may also show symptoms after exercise and/or heat stress. Without proper treatment MHS can be life-threatening.

Causes

About 70-80% of MHS is caused by harmful changes (called pathogenic variants) in the gene *RYR1*, and about 1% is caused by pathogenic variants in the *CACNA1S* gene. The remaining 20-30% is either caused by unknown genetic causes, or the MHS is a part of a specific genetic condition caused by pathogenic variants in other genes. For example, many neuromuscular disorders increase the risk for MH.

The *STAC3* gene has also been shown to cause MHS. Individuals reported with MHS due to pathogenic variants in the gene *STAC3* are often of Native American descent, and also have a condition called Native American Myopathy. This condition is inherited in an autosomal recessive pattern, so a pathogenic variant must be present in both copies of the gene.

Because individuals may not know that they have MHS unless they are exposed to one of the medications that can cause a reaction, estimating how common it is can be difficult. Current measurements include looking at the number of people who have had an issue during anesthesia with one of these medications, and were then found to have MHS. Those numbers show that approximately 1 in 5000 to 1 in 50,000 people are suspected to have MHS.

Diagnosing MHS

While genetic testing for MHS can be helpful to establish a diagnosis, medical providers may use another test, called a muscle contracture test (also called caffeine halothane contracture test, CHCT). This testing involves looking at a skeletal muscle biopsy (piece of

muscle that is surgically removed) after being exposed to substances such as caffeine or halothane (called ryanodine receptor agonists). Individuals who have MHS will have abnormally high levels of force in the contraction of their muscle biopsy sample when exposed to one of these substances.

CHCT may be considered in people who have a positive family history of MHS, a previous suspected episode of MHS, a history of severe muscle rigidity when exposed to one of the triggering substances, a history of moderate or mild muscle rigidity with rhabdomyolysis, history of unexplained rhabdomyolysis during or after surgery or after a negative rhabdomyolysis workup, or when there are other signs that increase the chance for MHS.

Unfortunately because there are a very limited amount of medical centers in the country that do CHCT testing, a majority of people will have to travel to one of these centers in order to have the testing done.

Medical Management

The main thing that is important for individuals with MHS to do for medical management is to avoid the gas anesthesthetic and succinylcholine that can cause a reaction. If someone who has MHS is having general anesthesia that goes on longer than 30 minutes, it is important to have their temperature monitored. It is also important for people who have a family history of MHS (and may also be at risk for it themselves) to let their medical providers know and to take the recommended precautions. There may also be other blood or urine tests that would be helpful to do when someone has just been diagnosed with MHS.

If someone is not known to have MHS but begins having a reaction under anesthesia, it is important for the medical team to be able to identify the signs early and begin treatment. If the episode is not caught early, more long-term damage to the patient's health can result.

Click here to learn more about scheduling a genetic counseling appointment for questions about pediatric or adult genetic conditions.

Additional Resources

Malignant Hyperthermia Association of the United States (MHAUS)

North American Malignant Hyperthermia Registry